

*NIH Disease Prevention
1990 Annual Report*



Office of Disease Prevention

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service · National Institutes of Health

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Introduction

The National Institutes of Health (NIH) has long been involved in prevention and prevention-related research. The mission of NIH is to acquire new biomedical and behavioral knowledge that ultimately will lead to better health for everyone. As a part of that mission, prevention research is intended to protect individuals from acquiring disease and to prevent the progression of disease to disability or death.

The wide spectrum of NIH research activities in prevention, for the purposes of this report, is described in the following four categories: basic research, applied research and clinical investigation, intervention studies, and professional and public education. These categories demonstrate the range of research efforts aimed at developing effective and safe preventive mechanisms and technologies for translation into health care practice. The program descriptions illustrate selective highlights of NIH research in prevention and consequently present only a fraction of NIH prevention efforts.

This report also contains figures for FY 1989 prevention research dollars and personnel.

Basic biomedical research encompasses experimental investigations aimed at discovering and advancing fundamental scientific knowledge. Immediate practical application of knowledge is not a direct objective of basic research; ultimately, the purpose is to marshal fundamental biomedical information to improve health and prevent and treat diseases. The following are some examples of basic research studies that are expected to provide insights that eventually can be used to prevent disease.

National Institute on Aging

Caloric Restriction and Increased Longevity

It is now accepted that the lifespans of laboratory rodents may be extended by up to 50 percent simply by reduced feeding. In the past decade, the mechanism(s) of such extension and potential clinical significance have been the subjects of intense research interest. However, no controlled studies to date have attempted to reproduce these findings in any species higher on the evolutionary scale than rodents. It is essential to determine whether the observed lifespan extension and concomitant preservation of physiological vitality is applicable to humans. The National Institute on Aging (NIA) is initiating, for the first time, primate models whose relevance to the human situation is much greater than that of rodents. The study is attempting to determine whether caloric modification of diets of rhesus and squirrel monkeys can affect aging rates as assessed by various physiological, biochemical, and behavioral indices.

After 1 year of full 30 percent caloric restriction, both the rhesus and squirrel monkeys appear to be quite healthy. Rates of weight gain are approximately proportional to food intake, and food consumption studies reveal that most diet-restricted monkeys are eating roughly 70 percent as much as their counterparts of comparable body weight whose diets are unrestricted. Dietary effects, if they occur, may be observable within the next several years.

Risk Factors for Health and Functioning in Old Age

The NIA-supported research has documented the importance of health behaviors and social factors for morbidity and mortality, even for those in the older ages. The relationship of previously documented risk factor relationships for specific chronic conditions is now under investigation. Research also is examining the different effects of risk factors on men and women, specifying the determinants and consequences of changes in risk factors over time, and demonstrating the importance of subjective versus objective measures of health.

Comprehensive analyses of data from the Alameda County Study have documented how changes in behavioral, social, demographic, and psychological risk factors are related to improvements or declines in health status for older persons. Further, examination of the "natural history" of risk factors indicates that behavioral, social, and psychological factors are highly interdependent and that successful interventions will be needed to address the complexity of these interactions. For example, those who smoked or were overweight tended to show greater declines in physical activity over time compared with those who did not smoke. Moreover, changes in some risk factors influence the development of other risk factors. For example, those older smokers who quit showed significantly less decline in physical activity levels than did those who continued to smoke.

Baltimore Longitudinal Study of Aging

The Baltimore Longitudinal Study of Aging (BLSA), now in its 32nd year, provides a means to evaluate the natural history of the effect of health promotion on improving health and preventing disease. Subjects in the BLSA are well educated and are concerned about their health. Over the past 30 years, most of the participants have worked to lower their cholesterol levels, stopped smoking, altered their dietary intake, and increased participation in exercise. Longitudinal data on these individuals are being used to examine the effects of changing lifestyle on their health and mortality. Survival analyses procedures are being used to understand

the importance of age on specific risk factors for morbidity and mortality. These survival studies are being combined with analyses using the Health Risk Appraisal program developed by the Centers for Disease Control and the Carter Center to predict longevity. Together, the studies argue that the importance of risk factors needs to be understood, both singly and in combination, and that the effects of time may in turn complicate the story. Also under examination are those factors critical in understanding why the men in the BLSA live, on the average, 8 years longer than the general male population.

National Institute of Allergy and Infectious Diseases

Vaccine Development for Sexually Transmitted Diseases

An estimated 4 million new cases of genital chlamydial infections and 2 million new cases of gonorrhea occur each year in this country. Since 1986, the number of cases of syphilis, one of the oldest known sexually transmitted diseases (STD), has dramatically increased. In light of the devastating impact of STD's on the health of women and infants and the role of STD's in HIV transmission, ongoing basic research is directed toward vaccine development, particularly for pathogens such as gonorrhea, chlamydia, and syphilis. Research on gonorrhea and syphilis continues to unravel the detailed structure of the outer membranes of these bacteria and their role in the infectious process.

Chlamydial Infection

Intramural researchers made significant progress toward developing a vaccine to prevent chlamydial infection when they identified the portions of the major outer membrane of chlamydia that stimulate protective antibodies. The DNA segments that control production of these regions were isolated and inserted into a vaccine strain of polio virus. Testing of this vaccine in nonhuman primates is the next step in the development process.

Genital Herpes

Another STD, genital herpes, affects an estimated 30 million Americans, and approximately 500,000 new cases of this recurrent, incurable viral disease are identified each year. Severe complications such as premature birth, intrauterine growth retardation, and congenital infection occur in 40 percent of babies born to mothers who have their primary

herpes infection during pregnancy. In addition, like syphilis and other genital ulcer diseases, herpes appears to facilitate transmission of HIV.

Considerable progress has been made toward the development of a safe and effective vaccine for genital herpes simplex virus (HSV) infection. Preliminary results of a clinical trial testing the safety of a recombinant HSV type 2 (HSV-2) glycoprotein vaccine in patients with recurring genital herpes suggest that the vaccine is well tolerated and immunogenic. Once researchers have broadened their knowledge of this vaccine, they will conduct a controlled trial to test whether enhanced immunity to HSV-2 elicited by the vaccine diminishes the frequency or severity of recurrent genital herpes.

Development of HIV Vaccine

A major problem confronting AIDS researchers is that HIV causes disease only in humans. Therefore, researchers examined other virus-induced immune deficiency diseases in animals similar to HIV infection in humans. It was discovered that the structure of the simian immunodeficiency virus (SIV), which infects certain monkey species, is closely related to the structure of HIV. The development of the SIV model for HIV infection and disease has created many opportunities to evaluate vaccine candidates for preventing AIDS. Recent results of vaccine development studies in animal models show promise for a vaccine against HIV infection. In a series of experiments with monkeys, researchers successfully used whole but inactivated SIV as a vaccine. Findings indicate that, at least in animal models, the immune system could be stimulated to resist SIV. Researchers hope to correlate such findings from animal studies to the human immune system and HIV infection.

Another approach to HIV vaccine development is the use of recombinant DNA technology. Researchers have developed a vaccine of purified envelope protein (gp160) derived from the genetic material of HIV. Early trials conducted by intramural researchers assessing the efficacy of the vaccine have demonstrated that it causes the development of antibody and T cell responses to many of the HIV strains. These results show that the vaccine has the potential to stimulate the immune system to react to HIV.

Hepatitis A Virus Vaccine Development

Hepatitis A virus (HAV), which causes acute liver infection, is transmitted by contaminated food and water. In 1988, more than 28,500 cases of hepatitis A were reported in this country. Serologic evidence of previous HAV infection occurs in

about 40 percent of our urban population. Several approaches to the development of a vaccine for HAV are being pursued.

Intramural scientists have developed a live vaccine that is ready for safety and immunogenicity testing in humans. In addition, NIH is supporting the development of a vaccine using recombinant DNA technology. Other research has identified two amino acid changes that are important for neutralizing HAV with antibodies. Research also has defined the properties of HAV necessary for growing the virus in tissue culture, an important step in vaccine development.

Bordetella Pertussis (Whooping Cough)

Although a pertussis vaccine was developed more than 40 years ago, recent concern about the rare side effects of the whole cell *B. pertussis* vaccine has stimulated research on the design of a safer vaccine. Current studies address the development and testing of nontoxic acellular vaccines that will be safer and at least as effective as the current whole cell vaccine. The protective efficacy of two acellular pertussis vaccines was established in a multicenter, placebo-controlled, double-blind study in Sweden; however, the clinically based efficacy and the safety of these vaccines require further study.

Research on the development of recombinant DNA-derived pertussis vaccines has progressed significantly in recent years. The development of a genetically detoxified pertussis molecule with the same immunogenic properties as native pertussis toxin is a significant advance that may lead to a useful vaccine in the future.

Renal Transplantation

Matching for antigens of the HLA major histocompatibility gene complex has been recognized as an ideal criterion for selecting donors for kidney transplants. When histocompatibility differences exist between a donor and a recipient, the recipient's immune response must be modulated or suppressed for the transplant to be accepted. However, because many immunosuppressive drugs are associated with serious side effects when used on a long-term basis, their overall usefulness is limited. New developments in immunosuppressive regimens should improve the success rates for kidney transplantation.

A recent study has succeeded in producing a specific state of acquired immune tolerance in kidney transplant patients. The use of total lymphoid irradiation on prospective patients for cadaveric kidney transplants induced a specific tolerance

for the histocompatibility antigens of the transplanted organs. This pretransplantation regimen allowed investigators to withdraw standard immunosuppressive drugs from three patients who were experiencing serious side effects to the drugs without jeopardizing the kidney transplant. This finding represents the first documented instance of induced transplantation tolerance in humans.

National Institute of Arthritis and Musculoskeletal and Skin Diseases

Detection of HIV in Skin Grafts

The use of donor skin to cover wounds in severely burned patients is generally a safe and effective therapy. Transmission of HIV by grafted skin, however, has been reported. Using a new methodology, polymerase chain reaction (PCR), a technique has been developed that makes it easier to detect HIV in small skin specimens. This method now can be used for screening donor skin graft material for the virus. The PCR technique is expected to become more widely available in the future, thereby ensuring a safer supply of skin for the treatment of burned individuals.

National Cancer Institute

Basic research is fundamental to the entire National Cancer Institute (NCI) program and shows promise for identifying the mechanisms of cancer development, and consequently, prevention. For example, there is continued progress in understanding basic biology as indicated by the rapid advance of knowledge in the field of carcinogenesis, the role of oncogenes, suppressor genes, and physiological growth factors, and in understanding the role of some viruses in causing cancer.

Genetics and Cancer

Genetic discoveries also are important to future cancer prevention. Recent discoveries include the location of abnormalities of chromosome 17, believed to contribute to the suppression of lung, colon, and breast cancers; the identification of at least six abnormalities or events that may be involved in the development of lung cancer; the location of the gene responsible for familial malignant melanoma on chromosome 1; and the identification of five proteins

produced by various genes important in metastasis, all paving the way for new treatments to prevent or inhibit the spread of cancer.

Calories and Cancer

During 1988-89, NCI launched a laboratory-based intramural effort in cancer prevention. The intramural Laboratory of Nutritional and Molecular Regulation has been initiated to investigate the possible interactions between energy intake (calories) early in life and cancer. The initial work in animals will lead to clinical metabolic studies concerning the relationships of a number of nutrients and calories to neoplastic changes in man.

National Institute of Child Health and Human Development

AIDS

As the AIDS epidemic continues to spread, NICHD places special emphasis on pediatric, adolescent, and maternal AIDS. Because children are primarily infected through their mothers, the Institute is conducting a variety of studies of AIDS in infants, children, and mothers. The NICHD issued a Request for Applications (RFA) on the role of the placenta in the transmission and treatment of HIV infection. The purpose of this RFA is to strengthen the basic research effort directed toward a better understanding of the role of the placenta in the transmission of HIV infection from mother to infant and its role in potential in utero therapies for HIV infection.

National Institute on Deafness and Other Communication Disorders

Vaccines and Hearing Loss

A large-scale project is concerned with management of otitis media, the most common cause of acquired hearing loss in children under age 10. A major prevention focus is being undertaken specifically through development of vaccines, to develop immunity against the most common pathogens responsible for acute otitis media. Successful development of a vaccine effective against as few as three major pathogens would reduce the incidence of acute otitis by as much as one-third.

Relationship of Smell to Neurodegenerative Diseases

The olfactory nerve can serve as a pathway for some pathogens and toxins to enter the brain from the nasal cells. Some studies suggest that certain neurodegenerative diseases, such as Alzheimer's and Parkinson's, start in this way. More recent studies in which olfactory threshold and identification tests were used indicate that the majority of Alzheimer's and Parkinson's patients have impaired smell function that manifests itself before the typical symptoms of the diseases appear and that there is no difference between the olfactory test results of the two types of patients. This finding is consistent with the hypothesis that both diseases have a common origin. Of special interest would be determining the etiology of the diseases in the few patients who do not have problems with smell function. This line of research has important implications for the early diagnosis of the diseases and, if their causes can be determined, for their prevention.

National Institute of Dental Research

Oral Physiology

Through support of an Aging Research Center, as well as studies by intramural and extramural scientists, the National Institute of Dental Research (NIDR) is improving the understanding of the mechanism of saliva in the maintenance of oral health. Specifically, research is considering the etiology of salivary gland dysfunction and its effects on oral tissue in aging individuals or those with alterations in normal functioning.

Periodontal Disease

Basic research is providing results that will help in the prevention of periodontal diseases. The NIDR research projects are evaluating the inhibitory effects of different antimicrobial agents against specific bacteria that have been implicated or associated with destructive periodontal diseases. Investigators at the Periodontal Diseases Research Centers, supported by NIDR, are conducting research to identify host response factors that predict periodontal diseases and to determine the prevalence of periodontal pathogens in the mouth. Additional diagnostic strategies are being tested, including radiographic techniques, and preventive measures, including chemotherapeutic agents.

Diagnosis of Dental Disease

The NIDR is encouraging research to develop more accurate measures of early diagnosis of dental caries. The early and accurate diagnosis of oral diseases will permit the prompt use of preventive measures and early treatment. One research project uses the chemical parameters of saliva and microbiological assays of plaque and saliva in an effort to improve caries prediction. Another project concerns the detection of incipient and clinical caries using optical technology. Another combines highlighted chemical parameters of saliva with more established microbiological assays of plaque and saliva to assess the caries-predictive properties of this battery of tests. Research is under way to create, develop, and test image-processing techniques designed to improve diagnostic performance. If successful, these tests would not only improve the treatment of individuals susceptible to caries but would greatly facilitate recruitment to large clinical trials.

Root Caries

With more adults retaining their teeth, the risk of root caries is an increasing concern. Research is under way to help understand the etiology of root caries within the context of clinical, microbiological, chemical, and immunological factors. Root caries experience is being compared over time in risk groups, including diabetics, chronic antibiotic users, individuals in areas with varying levels of water-borne fluorides, and individuals who restrict the intake of refined carbohydrates. The development of preventive measures for root caries is a priority.

Oral AIDS Diagnosis

Researchers supported by NIDR reported that by using a special DNA probe, HIV could be detected in gingival (gums) fluid just as readily as HIV antibody in serum could be detected by the traditional Western Blot test. This signifies that the earlier and more accurate the diagnosis of AIDS, the sooner therapy can be instituted, thus minimizing pain and discomfort to the patient. Additional research with saliva indicates that further isolation and characterization of the salivary inhibitory factor may contribute to the development of drugs to control the spread of AIDS and other soft tissue diseases having viral origins.

National Institute of Diabetes and Digestive and Kidney Diseases

Benign Prostatic Hyperplasia

Benign prostatic hyperplasia (BPH) is a commonly occurring disorder frequently and progressively seen in men over age 50. This gradual enlargement of the prostate gland causes variable degrees of bladder outlet obstruction. If permitted to progress without therapeutic intervention, it may have serious consequences, progressing from urinary stagnation to chronic kidney disease. The etiology of BPH is believed to be based on alterations in hormone balance associated with aging.

The male sex hormone most likely to be responsible for the growth and secretory activity of the prostate is 5 alpha-dihydrotestosterone (5aDHT). Steroid hormones like 5aDHT regulate cell function and biological activity (including growth/hyperplasia) by interacting with specific receptor proteins located on the surface of the target cell. Without such receptors, which bind a specific hormone to a given target cell, no effective hormonal stimulus is exerted on the tissue involved—such as would lead to unfettered growth of the prostate gland with advancing age. During the past year, investigators have been able to isolate, test, and partially analyze the structure of the DNA in prostatic cells, which is responsible for the production of the androgen-receptor that specifically binds 5aDHT, but no other steroids, to the cells. This major advance is essential for productive research aimed at future control of the abnormal growth of the prostate. It lays the foundation for controlling androgen-receptor protein synthesis, thereby enabling or disabling the mechanism that must be intact to permit prostatic growth and, in advanced age, prostatic hyperplasia.

National Institute of Environmental Health Sciences

Toxicity Testing of CFC Replacements

Ozone has been characterized as the single most important trace gas in the Earth's upper atmosphere. The reasons for this are that the particular ultraviolet radiation absorbed by ozone (biologically active ultraviolet, or UV-B) is especially damaging to animal and plant cells' structure, and the distribution of ozone throughout the upper atmosphere has

major implications for global climate. The ozone layer in the Earth's stratosphere—the area 6 to 30 miles above the Earth's surface where 90 percent of atmospheric ozone is concentrated—is thus essential to life on Earth.

In 1974, two theories were advanced that suggested potentially grave damage to the ozone layer. According to one of the theories, the release of chlorine into the atmosphere could unleash a complicated process that would continually destroy ozone for decades. A single chlorine atom was capable, through a catalytic chain reaction, of eliminating tens of thousands of ozone molecules. The other theory postulated that manmade chlorofluorocarbons (CFC) would break down in the stratosphere, releasing their chlorine and destroying the ozone layer. These hypotheses greatly concerned environmental and public health officials and industries that produce and/or use CFC's.

CFC's are widely used as coolants in refrigerators and air conditioners, as propellant gases in spray cans, and as "blowing agents" in the manufacture of plastic-foam material such as Styrofoam. They are inexpensive to manufacture and are not toxic. Production of CFC's had soared from 150,000 metric tons in 1960 to more than 800,000 metric tons in 1974, reflecting their broad usefulness. CFC production has remained constant since 1974.

CFC's, unlike many other manmade gases, do not degrade or "rain out" quickly in the lower atmosphere but rather migrate slowly upward into the stratosphere. Thus, millions of tons of previously produced CFC's are making their way to the ozone layer. If CFC uses were curtailed and emissions were to level off or decline, CFC's would continue to accumulate in the stratosphere for many decades, resulting in the future depletion of the ozone layer. Halons, frequently used in fire prevention, represent a related family of chemicals that has similar properties but is not as widely used as CFC's.

In 1986, an assessment sponsored by the National Aeronautics and Space Administration, the United Nations Environment Programme, the World Meteorological Organization, and other agencies concluded that continued CFC emissions at the 1980 rate would reduce global average ozone by about 9 percent by the latter half of the next century, with much larger changes depending on season and area of the globe. High levels of UV-B radiation would thus be reaching heavily populated regions of the Northern Hemisphere. New measurements also indicated that accumulation

of CFC's in the atmosphere had nearly doubled between 1975 and 1985, even though production of these chemicals had leveled off over the same period, illustrating the potential long-term danger from these substances.

Based on predicted future ozone depletion and increased UV-B exposure, the Environmental Protection Agency (EPA) estimates that in the United States alone there could be more than 150 million new cases of skin cancer by the year 2075, resulting in more than 3 million deaths. Other possible effects include eye cataracts, damage to the human immune system, serious effects on agriculture and fisheries, increased urban smog, and global climate warming.

Scientists supported by NIH are looking at how ultraviolet radiation damages the genetic material DNA and how skin cells repair that damage. Understanding the mechanism of injury could help in finding ways both to block ultraviolet damage and to repair the injuries.

If society stops using CFC's altogether, however, we must question the human health consequences of proposed replacements, a question the National Institute of Environmental Health Sciences (NIEHS) scientists can help answer. The NIH toxicologic studies of chloromethane and bromoethane, two potential replacements for CFC's, indicate that the compounds cause cancer in animal models. These findings suggest more information on potential human health effects is needed before those compounds are widely used.

Ozone and Skin Cancer

One of the technologies being seriously considered as a temporary replacement for the ozone-depleting CFC's is the development of the hydrochlorofluorocarbons (HCFC). Through the replacement of at least some of the chlorines of CFC's with hydrogen, it is possible that the compound will break down at the Earth's surface and prevent chlorines from reaching the stratosphere where they damage the ozone. Available toxicological information on HCFC's is limited. HCFC-22 is one of the few HCFC's studied. A long-term bioassay by the NIH/National Toxicology Program showed no increased risk of cancer in rodents associated with the compound. Because of rodents' metabolic characteristics, however, a wide range of additional toxicological and biochemical studies is needed. Moreover, little is known about undesirable ecological potential effects from HCFC's.

National Institute of General Medical Sciences

Cyclosporin A in Transplantation Therapy

As organ transplantation becomes more routine, the major complication is no longer the surgical procedure itself but the immune response of the patient to the new organ after surgery. For many years, the only immunosuppressive agent available, azathioprine, exhibited the severe toxicities associated with most antimetabolites, and thus its usefulness was diminished. The discovery of cyclosporin A as an effective immunosuppressant virtually revolutionized transplantation therapy. It is largely due to the availability of this drug that liver, heart, lung, and pancreatic transplants are as common now as kidney transplants were for many years. Recently, the drug has proven effective in the treatment of various autoimmune and inflammatory disorders and in nonmalignant proliferative disorders such as rheumatoid arthritis and psoriasis. However, its use is associated with toxic side effects to the central nervous system, kidneys, and liver. Investigators are examining the molecular structures of cyclosporin A and other immunosuppressants to determine which portions of their structures account for the toxic side effects. Others are examining the nature of each toxic phenomenon to determine which step(s) in the toxic reactions might be susceptible to inhibition. This research may yield information useful in designing new immunosuppressive agents, the toxic effects of which are minimized or eliminated.

Genetics Research

A group of researchers supported by the National Institute of General Medical Sciences has discovered an unexpected connection between cholesterol synthesis and the ability of an oncogenic (cancer-inducing) protein found in colorectal and pancreatic cancers to trigger cell division. This finding is the first to link cholesterol synthesis and the initiation of cancer. It not only helps scientists understand the processes that lead to cancer but also has prompted the idea that cholesterol-lowering drugs might find a place in the anti-cancer therapeutic arsenal.

National Heart, Lung, and Blood Institute

Familial Hypertrophic Cardiomyopathy

Familial hypertrophic cardiomyopathy (FHC) is a disease of the heart muscle that kills a significant number of young

people every year. This is the most common abnormality found in the unexplained deaths of young athletes. During the past 30 years, the cardiac features of the disease have been extensively reported, but the etiology and pathogenesis remain obscure. To understand the genetic basis for FHC, workers at Brigham and Women's Hospital in Boston, Massachusetts, have used genetic linkage analysis to identify the disease locus on human chromosome 14. This is a first step in providing direct access to the defective gene and will allow its identification, cloning, and sequencing. Such information will, in turn, lead to a determination of the specific biochemical nature of FHC, and the genetic marker may be used to identify asymptomatic individuals at risk for the disease. The design of effective prevention strategies will be the direct outcome of these findings.

Renin-Angiotensin System Role in Hypertension

Hypertension, or high blood pressure, is a major risk factor for the most commonly encountered forms of heart and blood vessel diseases. It is the single most important contributing factor to the development of stroke, and it accelerates the development of atherosclerosis in the coronary and peripheral arteries. The renin-angiotensin system, through a series of reactions, produces a powerful substance called angiotensin II, which can cause marked constriction of blood vessels. This system can play a prominent role in the physiology, pathology, and drug treatment of hypertension. Previously developed drugs that work on the renin-angiotensin system, although effective in lowering blood pressure, have had some undesirable side effects because their actions were not highly specific. Another approach now has been developed. Synthetic peptides are used to produce antibodies that can recognize the entire human renin molecule and inhibit its activity. This approach may lead not only to more specific antirenin drugs but also to potential vaccines with specific activity in inhibiting the renin-angiotensin system in hypertensive individuals.

Prevention of Thrombosis Through Interference With Platelet Aggregation

Thrombosis—the formation of a clot within a blood vessel—is the immediate cause of most heart attacks and strokes. Platelets, components of the blood important to clot formation, play an essential role in thrombosis and are a key factor in determining the efficacy and speed of thrombolytic (clot dissolving) therapy. To participate in these processes, the platelet must activate a cell surface molecule that

subsequently must bind to a large adhesive protein. Investigators have developed new monoclonal antibodies that bind to the activated surface molecule and peptides that mimic the large adhesive protein. These new agents are excellent inhibitors of platelet aggregation that may selectively and reversibly block the ability of platelets to form thromboemboli without producing acute toxicity or impairing long-term hemostatic function. In addition, these agents permit faster thrombolysis and prevent reocclusion after thrombolysis.

Hereditary Protein Deficiency

Protein S is an essential anticoagulant factor that prevents thrombosis. Thus, patients with protein S deficiency have a predisposition to thrombotic disease. The genetic lesion responsible for defective protein S function has recently been identified in three protein S-deficient families with hereditary thrombophilia. It was shown that a single base mutation in the protein S gene gives rise to a mutant form of the protein, which is unable to bind to its regulatory protein. Mutant proteins that are recognized as defective are then cleared from circulation, resulting in a deficiency. These findings demonstrate one mechanism of protein S deficiency which, in the homozygous state, is fatal. Because the human gene for this protein has been cloned, therapy with recombinant protein S is now possible. Such therapy is expected to reduce morbidity and mortality in infants with hereditary protein S deficiency.

Neuroactive Peptides and Hypertension

Our knowledge of the mechanisms by which the brain acts to control cardiovascular function has grown substantially in recent years. It has long been recognized that the release of adrenocorticotrophic hormone (ACTH) regulates the body's response to stress, but only recently has it become apparent that this response is also modulated by a class of substances known as the opioid neuropeptides. These substances serve to moderate the body's response to stress as well as to diminish pain perception. Young adults at risk for later development of hypertension show a pattern of exaggerated circulatory, sympathoadrenal, and behavioral responses to stress in both laboratory and naturalistic settings. The precise biobehavioral mechanisms of their activity remain to be identified, but recent findings suggest that defective opioid-mediated sympathetic inhibition may play a major role. Further research on the developmental pathophysiology of hypertension is expected to lead ultimately to the design of improved behavior therapies to reduce blood pressure.

National Institute of Neurological Disorders and Stroke

Isolation of the Gene for Neurofibromatosis

Recently, scientists reported the identification and isolation of the gene for neurofibromatosis 1, a genetic disease of the nervous system that affects one and a half million persons worldwide, about 100,000 of them living in the United States. The symptoms of the disease vary widely, with some victims suffering only mildly, showing dermal spots or benign lumps under the skin. In some patients, however, these lumps can grow large, a feature that prompted the disease to be named after the original 19th century "Elephant Man." The tumors can occur also on the optic nerve, sometimes leading to blindness, or may form in the brain, resulting in death. The course of the disease is highly unpredictable.

The most immediate benefit of obtaining the gene will be the ability to diagnose the disease early in its first stages, which previously has been difficult. Researchers believe that the detection of the gene will lead to better treatment of neurofibromatosis, which presently cannot be cured.

AIDS Vaccine Development

Scientists in the National Institute of Neurological Disorders and Stroke (NINDS) Laboratory of Central Nervous System Studies have collaborated with Dr. Jonas Salk, of the Salk Institute, on the development of a vaccine for AIDS. Studies focus on the potential therapeutic effects of an inactivated HIV-1 vaccine that lacks the viral envelope proteins. Scientists are inoculating chimpanzees to investigate strain variations for protection against infection and the nature of a long-term protective immune response.

Fogarty International Center

Malaria Model

Using a mouse malaria model, a Fogarty Scholar from Sweden, working with scientists at NIAID, clarified basic mechanisms whereby immune cells (CD4 and CD8 T cells) confer protection against malaria parasites. The development of immunity was found to be associated with the stimulation and proliferation of antigen-specific T cells and the secretion of interleukin-2 (IL-2) lymphokine. Because antigenic components of malaria parasites vary greatly in their ability to induce protective immunity, this information will be valuable in selecting antigens for incorporation in malaria vaccines.

Epilepsy

An International Research Fellow from Italy collaborated with researchers at the University of Maryland on the biosynthesis of quinolinic acid, an amino acid believed to play an important role in the pathogenesis of epilepsy. They clarified the mechanism for producing and releasing quinolinic acid in the brain and identified factors that regulate its concentration in nervous tissue. These findings could lead to the development of more effective prevention of epilepsy.

Calcium Studies

A Scholar from Switzerland defined basic mechanisms whereby intracellular calcium regulates a wide variety of physiological functions, including muscle contraction, electrical activity of cells, and intermediary metabolism. Such knowledge of the biological effects of calcium has broad applicability in medicine, for example, in the development of better cardiovascular drugs and anesthetics and in the prevention of musculoskeletal diseases.

Nicotine and the Central Nervous System

A Fellow from the University of Louisville, working with scientists at the University of Bath, studied the biochemical pathways through which nicotine affects the central nervous system. Their studies have led to a better understanding of the chemistry underlying tolerance to nicotine and have relevance to the prevention of nicotine addiction.

Memory Studies

A Fellow from the University of Alabama conducted studies at the Australian National University on relationships between the structure of nerve synapses (nerve-to-nerve connections) and their ability to transmit electrical impulses. The work has direct relevance to our comprehension of mechanisms involved in memory storage and to the eventual development of strategies to prevent memory deficits characteristic of Alzheimer's disease.

National Center for Research Resources

The Effect of Obesity on Pregnancy: Metabolism in Rhesus Monkeys

Pregnancy for obese women often is complicated by high blood pressure, toxemia, carbohydrate intolerance, and difficulties of giving birth.

The relationships between the mother's utilization of nutrients and her child's fetal development are difficult to study in human pregnancies for ethical and practical reasons. Because of the similarities between human and rhesus monkey pregnancies, monkeys represent excellent models for improving our understanding of these interrelationships.

Studies on approximately 100 well-controlled rhesus pregnancies have been completed. The mother monkeys were given glucose-tolerance tests during the third trimester of pregnancy and also when they were not pregnant. The mother's weight and fatness were measured as was the size of her offspring at delivery. This work led to five conclusions. First, increasing adiposity, or fatness, of the nonpregnant monkeys was accompanied by insulin resistance. Second, pregnancy also was accompanied by elevated insulin levels. Third, most glucose levels in the "average pregnancy" tended to be lower than in the same animal when nonpregnant. Fourth, increased adiposity at the time of conception was associated with greater chance of developing intolerance during pregnancy. It appeared that fatter mothers were unable to cope with the combined stresses of increased fat plus pregnancy. Finally, even mildly impaired glucose tolerance during pregnancy resulted in increased fetal growth. This increased growth was probably a consequence of fetal over-nutrition and stimulation of fetal growth factors.

In extreme cases, such as overt maternal diabetes during pregnancy, enhanced fetal growth is associated with a host of perinatal complications and may also produce long-term complications for the physical and psychological development of the offspring. Rhesus monkeys represent a valuable model for further study of the mechanisms of these problems as well as for possible therapies.

Genes and High Blood Pressure

Historically, the analysis of human pedigree data has been successful in identifying single genes that cause very rare diseases, each with a prevalence of less than 1 in 1,000. The more common diseases, with lifetime prevalences of 1 percent or more, appear to be due to a complex interaction of many environmental and genetic factors. Each single gene affects many different phenotypic traits. By analyzing these jointly, on pedigree data, it should be possible to identify the action of single genes. A statistical method of doing this has been devised, using the fact that all genes, when transmitted from one generation to the next, tend to cosegregate with other genes that are located close by on the chromosomes. An example is the recently proposed linkage between two

genes, one that controls diastolic blood pressure and related traits and another that controls 6-phosphogluconate dehydrogenase (a red blood cell enzyme). If such a linkage can be corroborated using more traditional parametric segregation and linkage analyses, this finding could eventually have a major impact on the treatment for hypertension. This new method of analysis will become increasingly important for the genetic study of common diseases as the human genome initiative progresses.

***Production of New Nerve Cells
by Growth Factors***

The nervous system is unique among body tissues in being composed of nonrenewable elements. Consequently, the

organization of the mature brain is dependent on the initial production of neurons. Knowledge of how this process is controlled may allow an understanding of how disease conditions produce deranged brain function and could lead to new therapeutic approaches to alleviate the symptoms of perinatal asphyxia and stroke, congenital spinal muscular atrophy, and neural tube dysgenesis. The primary functional elements of the nervous system, the neurons, are not produced during maturity, because neuronal mitosis (cell division) is restricted to early development. However, current studies indicate that insulin and insulin-like growth factors specifically stimulate entry of cultured neuroblasts into the mitotic cycle.

Applied Research and Clinical Investigation

Applied research and clinical investigation are more directed than basic research and involve individuals as well as total populations and subpopulations. A clinical trial is one form of applied research and is the primary mechanism for assessing the effectiveness of an intervention (prophylactic, diagnostic, or therapeutic agents, devices, or procedures). In disease prevention, applied and clinical investigators study measures to reduce the incidence of disease by reducing the risk of onset, reduce the prevalence of disease by shortening its duration through treatment, and reduce the prevalence of disease-induced disability by minimizing functional impairments. Following are some examples of applied and clinical studies supported by NIH.

National Institute on Aging

Influenza Vaccine

Ongoing National Institute of Aging (NIA)-supported research is attempting to define the most efficacious influenza vaccine and administration protocol for use in an elderly population. Influenza infections and their long-term adverse effects are a major cause of morbidity and mortality. More than 40,000 deaths per year have been reported in the elderly population in recent epidemics. This is due largely to the decline in the function of the immune system that occurs with advancing age, which results in a lower antibody response to a vaccine and lower levels of protection than in younger individuals.

The studies, carried out in healthy volunteers ages 65 to 83 years, are testing two types of vaccines given by different routes of administration: (1) a live attenuated influenza virus given intranasally and (2) an inactivated influenza virus given by intramuscular injection. The two different preparations were tested separately, and one group of subjects received both preparations simultaneously.

The effectiveness of influenza vaccination was quantified by measuring the rise in anti-influenza antibody levels at 1 and

3 months in serum and in nasal washings. The live virus given intranasally was not as effective as the inactivated virus given by injection in raising the serum antibody levels, and the highest levels were achieved in those subjects who received vaccine by both routes. The combined routes also resulted in the highest levels of antibody in nasal washings. There were no significant side effects from any of these protocols.

Influenza vaccination was effective in this study, with about half of the subjects showing at least a fourfold elevation in antibody titers both at 1 and at 3 months. Thus, the perception of the general population and of some physicians that vaccinations are ineffective in the elderly needs to be corrected. Only 17 percent of the adult U.S. population receives influenza vaccines. In the future, efficacious vaccines with low incidence of side effects will be provided so that increased participation of the elderly in vaccination programs can be expected to lower the current high morbidity and mortality from influenza.

Medication Use

Persons older than 65 comprise 12 percent of the Nation's population but consume more than 30 percent of the prescription drugs dispensed. Geriatric patients commonly suffer from multiple disorders for which they often take several medications whose side effects and interactions may diminish therapeutic efficacy and cause clinical problems.

The NIA is planning to support a broad spectrum of research relevant to the use and effectiveness of medications in older people. This includes basic and clinical studies on pharmacokinetics, pharmacodynamics, receptor biochemistry and physiology, drug metabolism and excretion, toxicology, pharmacotherapy and pharmacoepidemiology, as well as studies of techniques to improve quality of prescribing and utilization review. Studies of the effects of drugs and drug combinations in patients with multiple disorders are especially relevant to geriatric medicine. Studies related to prescribing practices, drug utilization review, and education of providers and patients are also of interest. Given the tendency of many older persons to accumulate a number of

chronically used drugs, there is a need for research-based guidelines for the withdrawal of medications from older persons so that only those medications required are continued.

National Institute of Allergy and Infectious Diseases

AIDS

A multicenter drug trial has shown that zidovudine (AZT) significantly delays the progression of disease in certain HIV-infected persons who have not yet developed symptoms. Another randomized, double-blind trial found that AZT also benefits patients in the early stages of symptomatic HIV infection. These studies have clearly shown the importance of early intervention in HIV-infected persons. Additional research is being conducted to determine if AZT, given at critical times, may actually prevent transmission of HIV.

Children born to mothers who are infected with HIV are one of the fastest growing populations of HIV patients. Very little is known about how or when HIV is transmitted from an infected mother to her child; therefore, the development of therapies that can either prevent transmission or block infection in babies of infected mothers is critically important. An extensive clinical trial under development will investigate whether HIV transmission can be prevented if a mother is given a dose of AZT just before delivery and the infant is given a dose just after birth.

National Cancer Institute

Smoking

Cigarette smoking is the major cause of lung cancer and an important risk factor for cancers of the oral cavity, pharynx, larynx, esophagus, bladder, kidney, pancreas, and other sites. In some parts of the country, smokeless tobacco (snuff) use accounts for a substantial portion of oral cancer, especially of the cheek and gum. Because tobacco products are responsible for a major portion of all cancers, studies will continue to define tobacco-related cancers, interactions of smoking and other possible cancer risk factors, and the extent of risk associated with various forms of tobacco exposure, including involuntary smoke inhalation (passive smoking).

Alcohol and Cancer

Studies have continued to evaluate the independent cancer risks associated with alcohol consumption and its effects in combination with other factors (e.g., tobacco and nutritional deficiencies). In a nationwide case-control study, heavy use of both cigarettes and alcoholic beverages resulted in greater than 35-fold increases in the risk of oral and pharyngeal cancers. Because previous studies suggested that the risk of breast cancer may be increased with moderate alcohol consumption, a multicenter, population-based, case-control study will continue to evaluate the role of alcohol intake as a risk factor (as well as oral contraceptive use, adolescent dietary patterns, anthropometric measurements, and endogenous hormones). In a study at Harvard University, a cohort of nurses is being followed prospectively to assess alcohol intake, long-term oral contraceptive use, and physical activity on the risk of breast cancer.

Occupation-Related Cancers

Epidemiological studies of occupation-related cancers are being pursued because they have proven to be an important means of identifying environmental carcinogens as well as industrial processes associated with increased cancer risk. An increased bladder cancer risk was found to be associated with the intake of chlorinated tap water, with long-term consumers having the greatest risk. To clarify these findings, a new case-control study is investigating cancer at six anatomic sites, including the bladder.

Pesticides and Cancer

Evaluation of cancer risks among occupational groups with pesticide exposure is a major focus of the National Cancer Institute (NCI). Several studies were prompted by elevated rates of lymphatic and hematopoietic cancers among farmers from several Midwestern states. In Kansas and Nebraska, the risks were especially high among farmers exposed to phenoxyacetic acid herbicides. These associations, particularly the relationship between non-Hodgkin's lymphoma and the herbicide 2,4-D, are being examined in further studies involving the agricultural use of pesticides.

Organic Solvents and Cancer

A number of projects are clarifying the association between cancer and exposure to various organic solvents. These investigations include a study of furniture workers and officers in the U.S. Coast Guard who are exposed to a variety of organic solvents while inspecting ships and barges. In China, a collaborative study of workers exposed to benzene and benzidine will clarify exposure levels at which these chemicals cause cancer.

Air Pollution and Cancer

The importance of air pollution in lung cancer continues to receive attention. A case-controlled study in Shenyang, China, where pollution levels from home-heating stoves and industrial sources are among the world's highest, continues to investigate the role of air pollution on the risk of lung cancer.

Ultraviolet Light and Cancer

Ultraviolet (UV) radiation is being investigated as an important cause of melanoma and nonmelanoma skin cancer. In melanoma, childhood and intermittent (recreational) exposures and sunburning are especially important, while in other skin cancers cumulative (occupational) exposures play a key role. Because sunlight is the major source of UV radiation and there is concern about stratospheric ozone depletion, UV exposures and skin cancer incidence are being monitored.

Chemopreventive Agent Screening Studies

Chemoprevention refers to the administration of chemical agents to prevent the sequence of events following exposure to a carcinogenic agent that results in the development of a malignancy. The NCI's Chemoprevention Program identifies and evaluates new compounds showing biological activity in experimental systems, synthesizes more potent and less toxic compounds, and initiates additional dose-setting and controlled clinical trials in chemoprevention.

The NCI now has 19 agents undergoing clinical testing, 250 agents in preclinical investigations, and 800 agents under review. A broad array of efficacy studies using animal models has been implemented to address breast, lung, colon, bladder, and skin cancers and to employ agents related to retinoids, beta-carotene, vitamin E, selenium, and other substances.

National Institute on Deafness and Other Communication Disorders

Learning and Language Disorders

Very young children who are late in reaching early language milestones (production of first words, growth of vocabulary, and combining words) may be at risk for later language impairment and/or learning disability. Research is ongoing to identify factors in children 18 to 24 months old that predict potential later language and learning deficits. This in turn will

allow appropriate early identification and referral. Profiles of language and other cognitive skills are being developed to serve as markers for those who are not likely to catch up linguistically. Data will be useful in identifying risk factors that predict language and/or learning impairment.

Articulation Skills

A longitudinal study is investigating the relation between the articulation skills of parents when they were children and the articulation skills of their children today. Two groups of individuals are participating: those who displayed significant and persistent articulation disorders in childhood and those who did not. The study is comparing the current speech and language skills, education, and occupational status of the two groups, as well as the speech and language skills of their spouses and children. This study will provide a better understanding of the factors that may contribute to the etiology of functional articulation disorders, a frequent speech disorder in preschool and school-aged children.

National Institute of Dental Research

Oral Health Survey

The National Institute of Dental Research (NIDR) has completed the nationwide 1986-1987 survey of schoolchildren. The summary report, *Oral Health of United States Children*, has been released, and additional analyses are being conducted. In addition to dental caries, the survey results are unique in including information for the first time on periodontal health, fluorosis (a condition produced by excessive consumption of fluorides during tooth development years), and soft tissue lesions. Also, information is available on use of smokeless tobacco and tobacco and alcohol, and salivary samples are available to assess the levels of disease-causing organisms.

The NIDR is supporting two longitudinal studies that will help assess the progression of oral diseases in relation to risk factors. Both the Iowa Study and Piedmont 65+ will provide essential data for analyses to improve understanding of oral health in older adults, individuals of lower socioeconomic status, and blacks.

Fluorides and Oral Health

Long-term clinical trials on the effects of combinations of fluoride regimens and the additive effects of dental sealants

in schoolchildren have been completed. Preliminary analyses indicate that all measures show reductions in caries. These reports will result in improved targeting for prevention of caries in schools and other preventive programs.

The NIDR investigators continue to evaluate the effectiveness of prenatal administration of dietary fluoride supplements to prevent dental caries in the primary dentition (infant's first teeth). The first 5 years of data gathering have been completed, and the data are being analyzed. The sample is being maintained for future investigations.

Although the value of fluoride has been well established, the importance of fluoride retention in the mouth is not yet clear. Research to study the relation between fluoride retention in plaque, saliva, enamel, and soft tissues and the clinical efficacy of home-use topical fluoride products is under way. Another project is aimed at developing a topical treatment procedure that can provide a complete or near complete elimination of both coronal and root surface caries without continued and/or frequent application. Specific emphasis is on methods that can effectively deliver the treatment agents to the sites that most need protection.

Prevention of Root Caries

Research supported by NIDR is investigating prevention of root caries, particularly the effects of fluorides on root caries. Attempts are being made to develop a less time-consuming topical treatment to eliminate root and coronal caries in adults. For example, adults over 60, who are at greater risk for root caries, are being followed over 4 years to assess the use of a daily fluoride mouthrinse or a semiannual topical application of a fluoride gel in preventing further root caries, to study the retention of fluoride in cementum (a covering on exposed root surfaces), and to assess the use of a glass ionomer and visible light-cured microfilled restorative system for the restoration of carious lesions on the roots of teeth. Other individuals at risk for root caries are those with overdentures because this technique uses prepared root fragments that are susceptible to periodontal diseases and caries. An experimental gel is being tested for comparison with a commercial fluoride gel for such individuals.

Periodontal Diseases

Prevention of periodontal diseases could be targeted best if disease activity were detected early. An array of potential biochemical and immunologic markers found in the gingival fluid may be useful in early detection of disease. Other approaches under development and testing include an electronic constant-force probe for the accurate measure-

ment of bone loss and a DNA probe kit to identify six known pathogens (organisms that cause disease) in samples of subgingival plaque. Also, using a study population in Sweden, NIDR scientists are investigating whether periodontal destruction, diagnosed in adults, could have been predicted from bite-wing x-rays taken at adolescence.

Other research projects are characterizing the pathogens and other risk factors, as well as the value of different preventive approaches, in groups at high risk for periodontal diseases. Study populations include patients infected with HIV, patients with diabetic complications, persons with insulin-dependent diabetes, users of smokeless tobacco, Navaho Indian adolescents, and Sri Lanka tea workers who receive no professional care.

Special healthy populations also are of interest in improving our understanding of preventive strategies. A group of Amish individuals who seldom brush their teeth or visit a dentist but who exhibit low levels of periodontal diseases is being studied to relate dietary intake to prevalence and severity of periodontal diseases.

International Oral Health Study

The NIDR is providing support for the International Collaborative Study II. A major focus of this project is to test the relative effects of socioenvironmental, delivery system, and personal and lifestyle factors on oral health behaviors and oral health status within and among 12 industrialized and middle-income countries and to develop a model to explain these determinants. These findings will assist in understanding strategies for prevention.

Oral Health Delivery Systems

The NIDR-supported research continues on the development of intraoral devices that slowly and continuously release low concentrations of therapeutic agents into the mouth to prevent and treat oral diseases. These are designed to deliver a therapeutic agent at a controlled rate to a specific site and are a safe and effective means of drug administration, especially appropriate for treating handicapped individuals. Experiments are being conducted with fluorides for caries, tetracycline and chlorhexidine for periodontal diseases, and antifungal agents for the prevention or treatment of diseases such as candidiasis.

Oral Health of HIV-Infected Individuals

A natural history study on oral conditions of HIV-infected individuals in a military population has been initiated as part of a larger natural history study conducted by the Army at

Walter Reed Army Medical Center. Also, within the Department of Veterans Affairs (VA), a surveillance system for documenting oral lesions, diseases, and treatment needs for HIV-infected individuals frequenting the VA dental clinics has been implemented as part of the VA national surveillance system. Both of these projects should help identify and prevent the burden of oral lesions associated with this condition.

Other Preventive Strategies

The feasibility of using newly developed plastic materials to arrest caries without cavity preparation and without the removal of the carious lesion is being tested. A 3-year test with 123 patients may establish that this conservative restoration approach represents a viable interim measure and may reduce the long-term consequences of caries.

National Institute of Diabetes and Digestive and Kidney Diseases

Screening for Prevention of Hemochromatosis

Hemochromatosis is an inherited disease in which the normal mechanism in man that prevents excessive absorption of dietary iron is defective. If the defect in this disease is derived from only one of the patient's parents, the individual will not exhibit clinical symptoms; however, if the defect is derived from both parents, the disease will manifest itself under the right circumstances. If the diet is rich in iron, the patient progressively will absorb more iron from his diet than he needs, which produces iron overload resulting in gray-bronze skin pigmentation, cirrhosis of the liver, diabetes (in 50 to 60 percent of patients), and progressive cardiomyopathy. Clinical signs of hemochromatosis occur infrequently before the fourth decade of life, indicating that a cumulative process is involved. The disease is ultimately fatal. A simple laboratory test has now been developed to determine the percent saturation of transferrin, which can identify individuals at risk before any clinical manifestation of the disease or significant iron loading of the body organs occurs.

Using this test, a large-scale screening study has been performed in 11,056 healthy Caucasian Red Cross blood donors. The frequency of the disease was found to be between 6 and

7 positive individuals per 1,000 male subjects screened and 3 positives per 1,000 women. Iron loss through menstruation, childbearing, and lactation is sufficient to explain the preponderance of male patients.

A major difficulty in dealing with idiopathic hemochromatosis has been the great diversity of symptoms and the lack of a simple screening test that could be used before organ damage takes place and clinical symptoms appear. This cumulative process *can* be prevented if the disorder is recognized early in life and prophylactic phlebotomy is instituted. The new test has the advantage of also providing some measurement of the degree of involvement in the individual. Including this new test among diagnostic procedures whenever blood is drawn provides the potential for preventing an ultimately serious and possibly even fatal clinical condition.

Prevention of Skeletal System Damage Due to Asymptomatic Hyperparathyroidism

The routine use of multiphasic screening tests has resulted in the detection of hyperparathyroidism (HPTH) in asymptomatic patients previously not suspected of harboring abnormal parathyroid activity. In the past, the diagnosis was made on the basis of symptoms of kidney stones, skeletal system involvement (progressive bone loss and fractures), peptic ulcer, mental status changes, or muscular weakness. With an increase in the diagnosis of asymptomatic patients due to comprehensive screening and improved assays for parathyroid hormone, it appears that the prevalence of HPTH may approximate 1 case per year per 1,000 for both men over 60 and women between the ages of 40 and 60 and 2 cases per year per 1,000 for women over 60.

Physicians are often uncertain about the management of patients with subtle or absent signs and symptoms but a clear biochemical diagnosis of HPTH. However, data are now available from several studies on the natural history of this disorder. A principal concern has been the possibility of progressive bone loss due to excessive parathyroid hormone, a particular problem in postmenopausal women at risk for osteoporosis. Some patients followed with sequential bone density determination have indeed shown substantial, progressive bone loss. Similarly, several studies of the rates of vertebral crush fractures suggest an increased frequency in asymptomatic HPTH compared with controls. Thus, it is generally recommended that if nonsurgical management is selected for patients with asymptomatic HPTH, bone mass must be monitored. Given the expense and time involved in

such monitoring, many physicians believe it is appropriate to operate on asymptomatic *young* patients with mild hypercalcemia and to undertake nonoperative management and followup in older patients.

A fall 1990 consensus conference on this subject is being planned by the National Institute of Diabetes and Digestive and Kidney Diseases in partnership with the Office of Medical Applications of Research, NIH. The purpose is to alert primary physicians to the much greater prevalence of asymptomatic HPTH than previously has been assumed. It is important to prevent what might otherwise become a serious cause for bone loss; such loss could occur independently or in dangerous concert with bone loss due to postmenopausal osteoporosis in women over the age of 45. The consensus conference will address the appropriate initial evaluation of patients with mild or asymptomatic HPTH and criteria for selection of cautious medical followup or parathyroid surgery with emphasis on optimal methods and frequency of followup evaluation, after diagnosis, for nonsurgical management.

National Institute of Environmental Health Sciences

Analgesic Use and Chronic Renal Disease

Chronic renal disease is another significant health problem. The U.S. Government spends about \$3 billion each year on dialysis for patients with end-stage kidney disease. Once kidney failure develops, there is currently no cure. It is therefore important to identify preventable causes of kidney disease. The National Institute of Environmental Health Sciences (NIEHS) scientists wanted to determine which environmental agents, such as chemical solvents, might be associated with increased risk of kidney disease. To answer this question, it was necessary to rule out other possible causes as well.

Analgesic Drugs and Kidney Disease

In the NIEHS kidney disease study, scientists found that daily use of the analgesic drugs phenacetin and acetaminophen may cause chronic kidney failure. Phenacetin, an analgesic that was once used in over-the-counter pain medications, has long been suspected to cause kidney problems. Phenacetin was removed from most pain medications in the late 1970's because of reports linking the drug with kidney cancer. Many medications that once contained phenacetin now have

acetaminophen, a chemically similar drug that is used in many popular aspirin-free pain medicines. The use of acetaminophen has increased dramatically in the past 10 years. The results of the NIEHS study suggest careful adherence to the recommended guidelines for using over-the-counter analgesics containing acetaminophen.

The epidemiologic study that demonstrated the link with daily use of acetaminophen-containing medications compared 554 adults with newly diagnosed kidney disease with 516 similar control subjects who did not have kidney problems. The kidney disease patients had been hospitalized at one of four medical centers in North Carolina between 1980 and 1982. The patients and the control subjects were asked about past use of pain medications and about other possible risk factors for kidney disease.

Those who took medications containing phenacetin every day for at least 1 year were five times more likely to develop kidney disease than those who took pain medications infrequently. Daily use of drugs containing acetaminophen was associated with a threefold increase in risk of kidney disease. Due to the biochemical similarities between phenacetin and acetaminophen, it is not surprising that these two drugs may affect the kidney in the same way. Both drugs have been shown to cause kidney damage in animal studies.

Daily users of nonsteroidal anti-inflammatory drugs such as ibuprofen and indomethacin also were more likely to develop kidney disease, although risk was primarily limited to older men or other groups with potentially compromised renal circulation due to other underlying conditions. No risk was found for daily aspirin use.

The NIEHS study is one of the first of its kind to find a link between regular acetaminophen use and kidney disease. Other studies need to be done to confirm this possible risk. If this finding holds true, then stopping overuse of acetaminophen might prevent at least 4 percent of chronic kidney disease.

This study does not indicate that occasional use of aspirin-free pain medications poses any danger of kidney disease. Use of these medicines for short periods was not associated with any risk in this study. Most over-the-counter medications come with the warning that if symptoms persist, the advice of a doctor should be sought. This is good advice and should be followed.

National Eye Institute

Prevention of Diabetic Retinopathy

Diabetic retinopathy is the most common eye complication of diabetes, a disease that affects an estimated 11 million Americans. It is the leading cause of new cases of blindness in the United States among persons ages 20 to 74 years. In diabetic retinopathy, the retinal blood vessels deteriorate and leak fluid into eye tissues. When this fluid collects in the macula, the part of the retina that provides sharp central vision, it causes macular edema, a swelling of the macula, and blurred vision. In some people, diabetic retinopathy progresses to a more advanced, proliferative stage in which abnormal blood vessels form on the surface of the retina. These fragile vessels can rupture and bleed into the eye or form scar tissue that contracts and causes retinal detachment. Both of these complications are sight threatening.

In 1985, the NEI-supported Early Treatment Diabetic Retinopathy Study (ETDRS) demonstrated that focal laser treatment (using the laser to seal the small leaky blood vessels in the macula) reduced the risk of vision loss from diabetic macular edema. In October 1989, the study released data showing that scatter treatment (using the laser to produce burns throughout nonmacular areas of the retina), combined with focal treatment for macular edema when present, effectively prevented severe visual loss in patients with moderate to severe nonproliferative retinopathy or mild proliferative retinopathy. Data showed no significant difference between early treatment and deferring treatment until patients approached or reached a more proliferative stage. Provided that careful followup can be maintained, study investigators concluded that it is safe to defer scatter treatment to a time when retinopathy approaches or reaches the high-risk stage of advanced new vessel growth.

The ETDRS scientists also had investigated the effects of aspirin on retinopathy. They concluded that two aspirins a day (650 mg) do not alter the progression of diabetic retinopathy and do not increase the risk of vitreous hemorrhage. Therefore, there is no reason for people with diabetes to avoid taking aspirin when it is needed for treatment of other problems.

Prevention of Blindness From Glaucoma

The first results of the NEI-supported Fluorouracil Filtering Surgery Study (FFSS) were reported in December 1989. This study is a multicenter, randomized clinical trial conducted to determine the effectiveness of the drug 5-fluorouracil (5-FU)

in improving the outcome of conventional glaucoma surgery in high-risk patients. Glaucoma is a disease characterized by an abnormal, progressive rise in fluid pressure inside the eye that gradually damages the optic nerve. Most patients are able to control their glaucoma with medications that either reduce fluid production or facilitate its overflow, but when these medications fail to reduce intraocular pressure, some patients need filtering surgery to provide a new fluid outlet to lower the pressure.

The FFSS was designed to determine whether postoperative subconjunctival injections of 5-FU of the eye could enhance surgical success by inhibiting scar tissue formation over the outlet incision that could block the fluid outflow. Although the study was not scheduled to end until 1990, patient recruitment was halted in June 1988 when it became evident that the combination of surgery and 5-FU therapy was significantly superior to surgery alone. In addition, two-thirds of the patients receiving treatment with 5-FU did not need to resume taking medications to control their glaucoma compared with one-third in the standard therapy group. Of those patients still requiring medication in the 5-FU group, fewer types and lower doses of medication were needed than for the standard treatment group. Patients will continue to be followed for the next 5 years to determine the long-term effects of this treatment.

National Heart, Lung, and Blood Institute

Familial Hypertension and Blood Cholesterol Disorders

Hypertension and blood cholesterol disorders cluster in families. Pathological processes that lead to hypertension, blood cholesterol disorders, or both may therefore involve shared genes, shared environmental factors, or a combination. Research on families living in Utah has led to the description of a new syndrome combining hypertension and cholesterol disorders that affects approximately 12 percent of patients with essential hypertension. The condition, familial dyslipidemic hypertension (FDH), has been demonstrated in a limited number of families, but the finding suggests that FDH may be present in 1 to 2 percent of the general population. Pedigree studies such as these are an essential first step in any attempt to understand the genetics of human hypertension or atherosclerosis, knowledge of

which will allow the design of strategies for prevention of these widespread diseases.

Mechanistic Basis for Differences in Hypertension Between Blacks and Whites

Previously, the extent and severity of hypertension in blacks were believed to be related mainly to limited access to health care. Recent experiments, however, indicate that there are physiological conditions that may be responsible. Two recent studies on children and young adults suggest that hypertension in black subjects is associated with elevations in peripheral resistance (the opposition to blood flow in the systemic circulation) rather than rises in cardiac output (the amount of blood ejected by the heart over time), as is commonly the case in whites. In a third study, investigators concluded that blacks and whites differ substantially in their responses to hormones that raise blood pressure. Such observations as these begin to provide a mechanistic basis for the differences in hypertension between blacks and whites that may lead to new specific and effective preventive measures against high blood pressure.

Echocardiography in the Elderly

Echocardiography permits the noninvasive measurement of heart structure and function. This technology is commonly used in cardiology for the diagnosis of valvular disease, cardiac structure abnormalities, and left ventricular hypertrophy. In 1979, the Institute's Framingham Heart Study began to use echocardiography to examine its cohort of more than 1,000 elderly men and women. The focus of this investigation was to measure left ventricular (LV) size (mass) in these active and healthy study participants. Subsequent followup of these individuals for cardiovascular disease, heart attacks, strokes, and congestive heart failure led to the conclusion that increased LV mass is an ominous risk indicator that, in many elderly people, precedes the onset of overt, clinically recognized cardiovascular disease. The association appeared to be much stronger than that found for "conventional" risk factors such as cigarette smoking and serum cholesterol level. In addition, the association was found in individuals who were not hypertensive. These findings suggest that pervasive and pathologic changes in LV structure occur in many people during middle age. Although many details about the consequences of these changes and their reversibility will be forthcoming, it is clear that echocardiography is a technological advance that has opened major new research opportunities for understanding myocardial pathology.

Raynaud's Disease

Biofeedback therapy recently has achieved notable success in the treatment of Raynaud's disease, a disorder of the sympathetic nervous system. Raynaud's disease is characterized by attacks of ischemia in the peripheral blood vessels, particularly those of the fingers and toes. The condition is marked by severe local cyanosis and pain, brought on by cold or emotional stimuli, and it is significantly more common in women than in men. In severe cases, drugs that dilate the vessels are prescribed, with limited success. Interruption of sympathetic nerve pathways also has been employed. In mild cases, no treatment is prescribed. Investigators now have shown that biofeedback training is effective in raising the temperature of the extremities by several degrees, and it can reduce the incidence of ischemic attacks by 80 percent, even 2 years after the initial training. Although no randomized trials comparing behavioral and pharmacologic therapy are available, pharmacologic treatment is thought to be effective in only 40 to 50 percent of cases. Given the success of biofeedback training in managing this disorder, it currently may be the treatment of choice.

Risk Factors for Recurrent Myocardial Infarction

The role of standard coronary heart disease risk factors in predicting the long-term risk of recurrent coronary events in survivors of myocardial infarction (MI) has been examined using the Framingham study data. In men and women who experienced an initial MI, returned for a baseline examination, and were followed for up to 32 years (mean = 9.7 years) for reinfarction or coronary death, age-adjusted, multivariate analyses showed that baseline systolic pressure, serum cholesterol, and diabetes predicted both reinfarction and coronary death. When adjustments were made for the effects of these variables, including age, the risk of coronary death was only half as great for women as for men. However, the risk of recurrent MI in women with diabetes was twice the risk in men with diabetes. Increased susceptibility to cardiac failure among diabetic women was an important factor in determining survivorship. Women with diabetes developed cardiac failure four times as often (16 percent) as women without diabetes (3.8 percent). Furthermore, when cardiac failure developed, 25 percent of diabetic women experienced a recurrent MI or fatal coronary event, more than double the rate when diabetes was absent. This study indicates that, in persons who recover from an initial MI, standard risk factors, particularly systolic blood pressure, serum

cholesterol, and diabetes, remain important determinants of coronary prognosis over many years and warrant attention in preventing subsequent events. In a diabetic patient who survives an MI, cardiac failure is a common occurrence and warrants early detection and vigorous management in association with appropriate control measures for the diabetes.

Racial Differences in Nicotine Metabolism

The Cardiovascular Disease Risk Factors in the Young Study (CARDIA) has produced new information on smoking, a major cardiovascular and pulmonary disease risk factor. Mean levels of serum cotinine, an indicator of nicotine exposure, were found to be significantly higher in black than in white smokers, despite that serum thiocyanate levels (another measure of cigarette exposure unrelated to nicotine) and estimated daily nicotine exposure were higher in whites. These differences persisted after statistical adjustment for age, sex, education, number of cigarettes smoked, their nicotine content, and frequency of inhalation. Higher cotinine levels (despite lower estimated nicotine exposure and thiocyanate levels) in black compared with white smokers suggest that there may be racial differences in the metabolism of nicotine or excretion of cotinine. These differences could be related to the higher rates of smoking-related illnesses and lower rates of smoking cessation among black smokers. Further research into nicotine metabolism and excretion and into the biologic mechanisms of nicotine addiction are needed to evaluate the practical importance of this finding. These possible racial variations in nicotine metabolism or cotinine excretion may be important and should be explored in developing smoking cessation strategies for children and adults.

Cigarette Smoking and Strokes

The effect of cigarette smoking on stroke incidence was assessed in the Framingham Heart Study. Regardless of smoking status or sex, hypertensive subjects had twice the incidence of stroke. Smoking was significantly related to stroke, even after age, hypertension, and other pertinent cardiovascular risk factors were taken into account. The risk of stroke increased with the number of cigarettes smoked. The relative risk of stroke in heavy smokers (more than 40 cigarettes per day) was twice that of light smokers (fewer than 10 cigarettes per day). Former smokers developed stroke at the same level as nonsmokers soon after stopping. Stroke risk decreased significantly by 2 years and was at the level of nonsmokers by 5 years after cessation of cigarette smoking.

National Institute of Neurological Disorders and Stroke

Deprenyl Treatment of Parkinson's Disease

This year, a National Institute of Neurological Disorders and Stroke (NINDS)-supported clinical trial revealed that treatment with the drug deprenyl delays the progression of symptoms in patients with early Parkinson's disease and postpones the need for L-DOPA therapy. This is the first time that we have evidence of a drug that can slow the progression of a neurodegenerative disease. Deprenyl also was found to increase significantly the time patients remained gainfully employed, a benefit that will yield increased productivity and annual savings in health care costs of millions of dollars. The findings are so striking that the trial was interrupted and modified to provide deprenyl to all patients in the continuing study. It now will determine the effect of long-term deprenyl treatment in association with L-DOPA therapy and the possible additional benefit of the antioxidant, vitamin E.

This trial was a major breakthrough for Parkinson's disease research, illuminating a mechanism for nerve cell destruction and providing support for a treatment to stop the attack. It also raises numerous questions about the applicability of the finding to other neurodegenerative diseases, such as Alzheimer's disease, Huntington's disease, and amyotrophic lateral sclerosis.

Drug to Improve Recovery After Spinal Cord Injury

Each year, 10,000 to 12,000 Americans incur injuries to their spinal cords, often resulting in some degree of paralysis, loss of sensation, or even death. Treatment, rehabilitation, lost income, Medicare, and other costs for spinal cord injuries approach \$8 billion annually. Adjustment to the lack of mobility, diminished sexual function, reduced urinary control, and loss of independence exacts a toll that is immeasurable.

The first treatment to improve recovery from spinal cord injury comes from the NINDS-supported National Acute Spinal Cord Injury Study. Patients who received the drug methylprednisolone within 8 hours of injury regained significantly more motor and sensory function than untreated patients or patients receiving another drug. For the many Americans who experience spinal cord injuries each year, early treatment with methylprednisolone will mean living more independently with less assistance from others. For

some, this will mean the difference between using a wheelchair or not. This breakthrough comes after years of testing different drug regimens to inhibit the secondary damage that occurs in the hours following initial trauma to the spinal cord.

Common Treatment for Febrile Seizures Found Ineffective

An estimated 4 percent of children between the ages of 6 months and 5 years experience seizures triggered by a fever. Physicians commonly prescribe phenobarbital to prevent recurrences of such febrile seizures. However, evidence from an NINDS study of phenobarbital showed that the drug does not prevent further seizures and, in fact, may inhibit intellectual development, as evidenced by lower IQ scores.

National Center for Nursing Research

Childhood Risk Factors for Cardiovascular Disease

The knowledge base for preventing heart disease includes the ability to identify high-risk groups on the basis of their risk factor profile and genetic predisposition. Early identification of these factors and longitudinal monitoring is needed. To achieve this, twin children and their parents are being studied to determine physiological (systolic and diastolic blood pressure, heart rate, serum lipids, and lipoprotein relative weight), behavioral (type A behavior and its components), and lifestyle (diet, activity, smoking) risk factors. Initial investigation indicates a heredity component in some of the physiological risk factors. Results of an ongoing study are expected to clarify the interrelationships among factors and the stability of these factors over time. Findings based on this research will provide the scientific knowledge on which to base appropriate interventions during childhood and adolescence.

Preventing Complications of Hormonal Imbalances

Increasing scientific data on the physiological basis of hormonally related disease conditions in women and developing interventions to alleviate suffering and functional disability are the purposes of several research projects currently funded by the National Center for Nursing Research. These studies are investigating symptoms related to menstruation, including a study that is examining accompanying gastrointestinal disturbances. In other studies,

investigators are seeking information on sleep disturbances in menopause and are describing the results of estrogen replacement therapy. Research findings on the correlations between physical activity and bone mineral density in women will assist in preventing osteoporosis, a severely disabling condition found in some women after menopause. Findings will also offer additional choices for management of common disabling symptoms and the prevention of further complications due to hormonal imbalances.

Fogarty International Center

AIDS International Program

Because AIDS has spread so rapidly across international boundaries during the past decade and to help stem this continuing global epidemic, cooperative multinational research training programs on AIDS were undertaken in FY 1988. The purpose of these programs is to increase the number of highly trained epidemiologists, postdoctoral scientists, and clinical investigators worldwide who can increase research efforts in AIDS, especially in developing countries where AIDS is epidemic and also in the United States. This international cadre of scientists also will be able to collaborate on research on the epidemiology and natural history of AIDS, wherever it occurs in the world, and conduct international clinical trials on new drugs and vaccines. The Fogarty International Center (FIC) developed a communication network to facilitate cooperation on international research and research training in AIDS.

The FIC International Training Grants in Epidemiology Related to AIDS Program trains foreign scientists from developing countries in epidemiology. Training is designed to increase scientists' capability for conducting epidemiological research related to AIDS in their home countries and for using epidemiology in prevention research and clinical trials of new drugs and vaccines. A total of 125 individuals from 22 developing countries began training under the first year of the epidemiology program. Of these, about 55 percent were from Latin America, 30 percent from Africa, and 15 percent from the Far East/Western Pacific area. In addition, 25 in-country courses were provided for more than 1,000 students in 12 countries through the epidemiology training program.

The FIC International Postdoctoral Research and Training in AIDS Program provides opportunities for advanced postdoctoral research training for U.S. and foreign scientists. The

training generally is at a more advanced level than that conducted through the epidemiology program. In addition, this program provides training for a wider range of disciplines, including clinical and laboratory investigations of the natural history and pathogenesis of AIDS. Special attention is given to the theory and practice of the conduct of clinical trials for new drugs and vaccines. Under the post-doctoral program, training began for 15 individuals from 10 countries.

Both programs support research training in the United States and the investigators' home countries and operate through FIC grants to U.S. institutions. Examples of research conducted through the FIC AIDS programs include the following:

- Research was conducted on the antigens of HIV-regulatory proteins and their use in seroepidemiological studies. The HIV-2 X protein was found to induce antibodies in some people and, when present, indicates that the infection is due to HIV-2 and not HIV-1. Blood tests to detect these antibodies are now used to determine the nature of the infection in patients suspected of having AIDS.
- Research was done on the cell-mediated immune response to HTLV-1 and -2, and antigenic components of these viruses are now being identified. These components are used in immunologic research to determine antibody-dependent cellular cytotoxicity and cytotoxic T cell activity. These studies have revealed the importance of immunity in the pathogenesis of HTLV-1 and -2 infections. Such information provides the rationale for vaccine development.
- Research was done on the mechanism by which HIV kills infected T lymphocytes. These studies are concerned with the accumulation of DNA strand breaks in HIV-infected cells and the processes through which this accumulation leads to the activation of "programmed cell death." Such research may lead to new methods to reverse the infectious process.
- Research was carried out on the epidemiology of maternal-fetal transmission of HIV-1, including the role of breast feeding. This is being done through a community-based study in Zambia that should serve as a prototype for similar investigations in other countries. Much more information is needed on this emerging

aspect of the AIDS epidemic, which is moving into previously spared population segments.

- Research is under way on the clinical and laboratory features of Kaposi's sarcoma, a debilitating aspect of AIDS that occurs in some AIDS patients. This research will evaluate the efficacy of various chemotherapeutic agents in treating this complication.
- Research is being done to develop new tissue culture cell lines for the production of retroviral glycoproteins. Scientists have learned that the production of the glycoproteins is increased if the cells are coinfecting with HIV and cytomegalovirus. This research may lead to new methods to prepare vaccines from the virus glycoproteins produced in infected cells.
- A Scholar from Nigeria, the first from Africa, is defining diseases produced by HIV viruses in Africa and comparing their extent and severity with those that occur in the United States where modes of transmission are different. Attempts are being made to isolate and identify possible variants of HIV in Africa, which have the potential for spreading to other parts of the world, to detect them early and to control them. A monograph is being prepared on the African perspectives of AIDS, which will be a valuable resource to American researchers.

The FIC will continue to support research on AIDS through its research and training programs, through support of the Third Pan American Congress on AIDS, and through continuing support of the International Network for AIDS Research Training. Research will include epidemiology studies in the trainees' home countries to further strengthen their efforts in combating their rapidly growing number of AIDS cases. Relations established between the U.S. and foreign investigators also will lead to long-term mutually beneficial research collaborations and will facilitate drug and vaccine intervention trials as these become feasible.

National Center for Research Resources

Health Effects of the Environmental Pollutant Methylmercury

Methylmercury, a chemical compound that slowly accumulates in the environment with the burning of coal and oil

products, has been designated by the International Program for Chemical Safety as one of the six most dangerous such substances. In high concentration, these pollutants are known to cause brain damage and death in adults. Researchers have suspected that lower levels of exposure might produce less noticeable but equally devastating effects. Recently, researchers completed a series of studies in monkeys showing that methylmercury at blood concentration levels well below 3 parts per million (PPM) produces major nervous system disorders and equally disabling effects of other kinds, including infertility, stillbirths, retarded growth, and mental retardation.

Studies of effects of methylmercury on pregnancy and mental development were conducted on monkeys because their reproductive system and brain structure are close enough to the human to make the findings highly relevant. The same kinds of psychological testing that have demonstrated mental retardation in the offspring of monkeys exposed to methylmercury can be used to test human infants. These studies provide the most reliable information to date on the levels of exposure at which abnormalities are likely to occur and indicate to researchers several specific kinds of abnormalities to look for in studies of humans exposed to the substance. Information acquired from these studies is now being incorporated into human epidemiological studies to measure relative health effects in various populations.

Prophylactic Effects of AZT

A variant of simian immunodeficiency virus (SIV) derived from a chronically infected pig-tailed macaque causes acute clinical disease and death in experimentally infected pig-tailed macaques. This animal model system, which should be extremely useful in the rapid evaluation of newly developed antiretroviral drugs, has been used in a preliminary study to evaluate the prophylactic effects of AZT when administered shortly after virus exposure.

Results from this study indicate that some protection is provided by AZT when treatment is initiated within 24 hours of exposure to an acutely lethal simian HIV-like virus. This preliminary study further documents the usefulness of this animal model in the rapid evaluation of antiretroviral drugs.

Natural Killer Cells and Macrophages in Immune Surveillance of Cancer

The long-term objectives of this research included the establishment of novel and effective alternative methods for treatment and prevention of cancer and immune deficiency diseases. The specific aims were to determine the importance of nonspecific mediators of cellular immunity, such as

natural killer cells (NKC) and macrophages, that ingest foreign particles or other cells, in tumor induction by a known carcinogen, 3-methylcholanthrene (3-MC). This was to be accomplished by depleting NKC and macrophage function with antibodies to these cells at selected times during tumor formation.

The principal investigator was able to demonstrate that enhancement of NKC activity did decrease tumor incidence and increase tumor latency in his chemical carcinogen 3-MC treated rat model. Further, he discovered a monoclonal antibody (MAB) that markedly stimulated NKC activity. Additional experiments have been designed to test natural cytokines (interleukin, interferon, enkephalin) that enhance NKC activity in conjunction with this antibody as potential immunotherapeutic regimens for treatment of cancer and immune deficiency diseases.

Sodium Fluoride to Prevent Osteoporosis

Approximately 5 million Americans suffer from spinal osteoporosis. It is estimated that half a million persons sustain fractures of the spine yearly, and one-third of women over 65 years of age have vertebral fractures. Spinal osteoporosis results from gradual loss of bone with menopause and aging, eventually causing crush fractures.

It has long been known that fluoride can stimulate bone formation. Fluoride seems to exert this action by increasing the concentration of ionic calcium in osteoblasts. Long-term treatment with sodium fluoride (NaF) has been shown to increase the mass of trabecular bone in the spine. Unfortunately, this treatment has been beset with serious complications. By reacting with gastric acid, fluoride may cause irritation of the stomach lining and bleeding in up to 40 percent of patients. Moreover, it may cause joint pain, swelling, and more serious stress fractures in up to 40 percent of patients. It has even been suggested that this treatment may cause hip fractures. These complications have been attributed to the formation of abnormal bone, which mechanically is not as strong as normal bone.

To overcome these problems, NIH-supported scientists at the University of Texas Southwestern Medical Center at Dallas prepared a special slow release formulation of NaF. Intermitent slow-release sodium fluoride plus calcium citrate provided safety of usage, relatively free of gastrointestinal side effects; produced continued augmentation of spinal bone mass; and stimulated formation of normal bone with

adequate mechanical properties. Most important, it prevented spinal osteoporosis fractures.

***Computer Management of Eye Disorders
in Developing Countries***

The Primary Eye Care Program is targeted to frontline health workers in developing countries. The objective of this project is to program a laptop computer to provide advice to primary health workers on the management of common, potentially blinding eye disorders in developing countries. In developing countries, blindness is a major health problem, the control of which depends on the application of simple measures by frontline workers. Unfortunately, in many of these

countries, medical care by physicians is not readily available. To assist primary health workers in the management of common and potentially blinding eye disorders, a prototype computer program was developed for a handheld computer that incorporates a set of guidelines for diagnosis and treatment. This effort is in collaboration with Dr. Chandler Dawson, who heads the WHO Center for the Prevention of Blindness and Trachoma, and the Proctor Foundation for Program Research in Ophthalmology at the University of California, San Francisco. During the past year, versions of the program were completed in English, French, and Arabic. Testing is under way in Tunisia and Egypt.

Intervention studies seek to determine whether a specified form of intervention such as screening, education, or other directed behavioral or medical therapy can prevent disease, disease progression, or disease consequences. The following examples provide a cross-section of the NIH-supported intervention studies.

National Institute on Aging

Effectiveness of Behavioral Interventions

Contrary to popular assumptions that older people are not willing or able to change their behaviors, research is showing that: (1) older people can be successfully recruited into health promotion programs, (2) programs based on theories of behavioral change processes can indeed be effective in modifying individual behaviors and lifestyle practices, (3) maintenance is often a problem, but older people are no less compliant to medical regimens than younger persons, and (4) organizational strategies can be designed to reinforce individual behavior change.

Rehabilitation of older persons is being enhanced by new models that combine psychosocial and medical approaches. For example, a "map" has been designed to guide the patient, family, and caregiver through the complicated recovery process for survivors of stroke. Also, depression is a key factor preventing recovery from hip fracture, but such psychological conditions are often ignored in the treating of conditions viewed as purely "medical."

Physical Frailty

Deficits in mobility, strength, and balance contribute to a frail physical state in many older individuals, resulting in functional limitations and injuries. The functional limitations can reduce the quality of life while increasing dependency and the need for long-term care.

Certain physical deficits in mobility, strength, and balance in older people appear to be partially preventable or reversible by lifestyle interventions, chiefly physical exercise and rehabilitation regimens. For example, National Institute on

Aging (NIA)-supported studies carried out in a cohort of very old (average age 90 years), frail persons in a nursing home show that 8 weeks of strength training more than doubled quadricep strength and increased muscle size.

The degree to which reducing physical frailty can increase functional ability and decrease injuries, such as falls, will be evaluated in a coordinated set of controlled pilot studies of biomedical behavior or environmental interventions. These studies were funded during FY 1990.

National Institute of Arthritis and Musculoskeletal and Skin Diseases

Lyme Disease

Lyme disease, which is caused by a tick-borne spirochete, is widespread with cases reported from the United States, Europe, Asia, Africa, and Australia. In the United States, the number of cases of Lyme disease diagnosed is increasing and appears to be spreading to new areas of the country. Recently, birds have been identified not only as important local reservoirs but also as long-distance dispersal agents for infected ticks. It has now been shown that migrating birds can carry the infected ticks. (White-tailed deer and white-footed mice are the primary reservoirs for the ticks that are responsible for transmitting the disease to man.) This new knowledge about an additional mode of disease transmission is important for the development of prevention and control strategies.

Osteoporosis

Approximately 1.2 million fractures each year in the United States are due to osteoporosis. Recent NIH conferences stressed the need to develop safe, effective, low-cost strategies, applicable to populations at large for:

- Maximizing adult peak bone mass.
- Minimizing bone loss.
- Preventing fractures.

Inadequate calcium intake is one of the important risk factors for osteoporosis. Factors that affect calcium absorption recently have been identified. The absorption of calcium supplements is greater when ingested with a meal rather than on an empty stomach. Further studies are under way to examine how various foods act and interact to promote or retard the absorption of calcium.

National Cancer Institute

Diet and Cancer

A variety of human diet and chemoprevention trials are under way, including a lung cancer prevention trial using chemoprevention agents with 29,000 subjects in Finland and a multiple vitamin and mineral-based study of the prevention of esophageal cancer among 34,000 subjects in China. A recent chemoprevention trial was aimed at determining the impact of high fiber on rectal polyp regression and development in patients at a high risk of colon and rectal cancer. The study showed that high fiber was associated with polyp regression and suggests that a dietary fiber grain intake of at least 11 grams per day may inhibit polyp development, which in turn, may reduce the risk of colon and rectal cancer.

The National Cancer Institute (NCI) is sponsoring human efficacy chemoprevention trials to determine the potential for chemoprevention methods and regimens to reduce cancer incidence, the incidence of specific cancers, and changes in cellular or biochemical parameters associated with tumor regression or progression. Several of the 12 ongoing trials focus on those at high risk for lung cancer. One study has begun involving former asbestos workers, most of whom are heavy smokers. The subjects are being given one of two dose levels of etretinate to evaluate changes in the level of monoclonal antibody 17.13. High levels of this antibody may be associated with the development of lung cancer.

Additional studies involve subjects at high risk for the development of colon cancer. These studies involve subjects with a previous colon adenoma, a lesion generally agreed to be a precursor for colon carcinoma.

A randomized, double-blind, placebo-controlled clinical trial is evaluating the efficacy of nutritional supplements in preventing neoplastic polyps of the large bowel in persons at high risk for this condition. This is a collaborative investigation conducted at six study centers with subjects who have had an adenomatous polyp removed within 3 months of the recruitment. Trial treatments are beta-carotene; vitamin C (ascorbic acid) and vitamin E (alpha-tocopherol);

and beta-carotene, vitamin C, and vitamin E. Another group of investigators recently has initiated a randomized trial to evaluate the role of dietary fiber and calcium in subjects at elevated risk of developing colon carcinoma. This trial could lead to a larger scale trial to determine the efficacy of these agents in lowering polyp recurrence rates. In addition, there are two ongoing trials that address cervical cancer. Each has the primary goal of evaluating the efficacy of chemopreventive agents in preventing the development of invasive cervical carcinoma in women with preneoplastic lesions of the cervix.

Sun Awareness Program

Because Arizona has the highest rate of malignant melanoma in the country, the University of Arizona Cancer Center has targeted this deadly skin cancer for a broad range of research. The cancer center also is conducting the Arizona Sun Awareness Project to provide information about the risk of overexposure to the sun, sunscreens, skin cancer screening, and treatment.

Smoking and Cancer

The NCI's Smoking, Tobacco, and Cancer Program has made progress on a number of fronts. Through a series of research studies, the program has shown that primary care physicians and dentists have great potential to reduce adult smoking behavior. The results of NCI's major physician-based intervention trials have been released in manuals, pamphlets, and a training program, all for national dissemination. Material also has been released to enable smokers to quit, and materials were developed and distributed nationally showing how media can be employed in smoking control strategies. Among other research, the program has demonstrated that smoking onset among 12- to 14-year-olds can be reduced by up to 80 percent through school-based prevention trials. The results of these trials have been prepared for national dissemination.

Research results from the Smoking, Tobacco, and Cancer Program led to the initiation, in 1986, of the Community Intervention Trial for Smoking Cessation (COMMIT). This randomized community-based trial involves 11 pairs of communities and more than 2 million people in the United States and Canada. The trial is testing a protocol of smoking cessation strategies delivered through community organizations and social institutions. It is aimed at heavy smokers—persons who smoke 25 or more cigarettes per day. The results of this major intervention study will provide a model to communities around the Nation.

Building on the experience of the COMMIT trial and the need to reach all smokers as well as prevent smoking, NCI launched, in 1989, the first steps toward the American Stop Smoking Intervention Study (ASSIST), a large-scale demonstration program to disseminate the results of NCI's smoking and tobacco programs. The study, now in planning and slated to begin in 1992, will involve 20 states or large metropolitan areas and will reach 50 million Americans. The program is being conducted jointly by NCI and the American Cancer Society.

National Institute of Child Health and Human Development

Learning Disabilities

Investigation of the causes and treatment of learning disabilities is progressing well. Researchers sponsored by National Institute of Child Health and Human Development (NICHD) studying dyslexia (inability to read, spell, and write words despite the ability to see and recognize letters) have amassed strong evidence that a chromosomal anomaly is linked to one or more forms of this learning disability. Further findings reveal that computer-aided instruction can be effective intervention for some forms of dyslexia. During FY 1989, the NICHD established two Learning Disability Centers: one at Johns Hopkins University and another at Yale University. In FY 1990, the Institute will fund another new Learning Disability Research Center.

Studies of Low Birthweight and Preterm Labor

Risk factors such as smoking, level of maternal education, restricted maternal weight gain, and a variety of obstetrical conditions do not explain the twofold increase in incidence of low birthweight babies among black women compared with white women in the United States, and reasons for large ethnic differences are unknown. To address these disparities, NICHD has launched a major research program in the prevention of low birthweight. This initiative includes a study to obtain data from pregnant women from five ethnic groups and a community-based intervention among predominantly black women in the District of Columbia. Researchers focusing on factors that play an important role in human parturition have found that *Mycoplasma hominis*, *Chlamydia trachomatis*, heavy smoking, and delivery of a previous low birthweight infant have been associated with preterm birth;

and chlamydia, *Candida albicans*, maternal smoking, and alcohol consumption have been associated with intrauterine growth retardation.

Adolescent Pregnancy and Childbearing

The NICHD continues to support research on the factors that cause teenage pregnancy, which remains prevalent and carries considerable potential risks to the health and welfare of both mother and baby. Studies show that youth who become sexually active early exhibit a pattern, including early physical maturation, low levels of religious participation/influence, low levels of parental education, single-parent family membership, low educational and career expectations, low academic achievement, and early participation in drug and alcohol use. Researchers are developing biosocial models of sexual behavior in adolescence, including biological and behavioral or sociological variables. Biosocial models are being designed to provide teenagers with better information about their susceptibility to becoming pregnant or causing pregnancy, the consequences of maternity/paternity, the benefits of fertility control, and the lowering of perceived barriers to fertility control.

Diabetes in Early Pregnancy

A variety of malformations occur more commonly in births to diabetic women; these can be determined in the first 6 weeks of life. To elucidate these issues, the NICHD-supported Diabetes in Early Pregnancy Project (DIEP) examined the relationship between maternal diabetic control during organogenesis (creation of embryonic organs) and malformations in the offspring, sought to identify the specific teratogenic factor or factors (which produce physical defects in the embryo) in the diabetic metabolic state, and compared early fetal loss rates in women with diabetes and control subjects. It was determined that women in both the diabetic and control groups who had a normal fetus at the 8-week ultrasound examination had an extremely small chance of subsequent miscarriage. In sharp contrast to earlier impressions, a second finding revealed no relationship between the level of glucose control during organogenesis and the risk for congenital malformations. All DIEP subjects had reasonably good glucose control; hence, any glucose-related malformation would not have occurred in this study population. This study demonstrates that there probably are other teratogenic factors associated with diabetes. Various other DIEP analyses are under way to assess further the relationship between diabetic pregnancy and fetal development.

The Content of Prenatal Care

The NICHD provided staff support to the Public Health Service Expert Panel on the Content of Prenatal Care, which presented its report, "Caring for our Future: The Content of Prenatal Care," on October 2, 1989. The report is the first expert evaluation of specific prenatal care activities. It specifies the content of prenatal care for women at medical and psychosocial risk as well as healthy women based on early (preconception) and continuing risk assessment. The report identified an extensive research agenda to fill gaps in knowledge and suggested full implementation of the report's recommendations to reduce infant mortality and morbidity in this country.

Preventing Low Birthweight

A current major study is designed to ascertain nutritional and other factors that account for the high rates of low birthweight among urban blacks. Nationwide figures for low birthweight are 12.5 percent for black and 5.7 percent for white babies. However, the rate for black babies in Washington, D.C., is 18 percent, and at Howard University Hospital it reaches 20.6 percent. Scientists have made some startling discoveries in a group of 680 pregnant black women living in Washington, D.C.: about 20 percent of them failed to gain during pregnancy the minimum recommended amount of 21 pounds; 46 percent of them have levels of serum ferritin below the normal range; and 30 percent of them have serum folate below the normal range. These nutritional findings are important because infant birthweight correlates significantly with folate intake during the second trimester of pregnancy. One of the most remarkable findings of this project is that the rate of low birthweight in the study population has dropped to 8.9 percent while the general rate for those delivering in the same hospitals is more than 20 percent. Being part of this study has been extremely beneficial for these pregnant women. An important challenge is to ascertain what particular factors in the study account for this improvement.

Intrauterine Growth Retardation

Low birthweight and infant mortality are areas of particular concern and emphasis within NICHD. Neonates, or newborns, with intrauterine growth retardation (IUGR) contribute disproportionately to perinatal morbidity and mortality. They are at increased risk for mental retardation, neurologic abnormalities, and reduced growth potential. There are some data to demonstrate whether IUGR, once diagnosed, can be arrested and/or reversed in utero. An

intervention study has demonstrated that maternal bedrest improves the status of the IUGR fetus and therefore may reverse IUGR and decrease perinatal morbidity and mortality.

Day Care

The quality and consequences of child day care are of concern to parents and institutions in both the public and private sector. The NICHD has undertaken a longitudinal, multisite study to investigate the effects of different types of day care (ranging from exclusive maternal care to extensive reliance on day care) on the social, emotional, cognitive, and language development of children. The project will take place over a 5-year period and will study children from birth to 3 years of age. A major strength of the project is the use of a common research protocol at each of the 10 sites.

Childhood Injuries

Childhood injuries pose a serious threat as the leading cause of morbidity and mortality from birth to adulthood. Prevention of childhood injuries is an NICHD priority, and the Institute has initiated a 5-year research plan to determine the mechanisms and factors related to safety and risk behavior. Included in this initiative is the development of new methodologies and standardized approaches for classification of variables essential for injury research data. Preliminary studies have demonstrated that mothers of children with a history of injury are more likely to sit passively or only interact with their children to stop an injury instead of actively teaching and directing them about how to prevent an injury. Injury-prone children also were more likely to encounter more hazardous situations and display more disruptive and overly active behavior than children in general. With these initial findings, researchers are proceeding with studies of how parents perceive injury risks for their children, how children's developmental stages relate to the likelihood of their sustaining injuries, and how teaching models can be developed to show parents how to prevent injuries.

National Institute on Deafness and Other Communication Disorders

Stuttering Therapy

A microcomputer-aided stuttering therapy program has been developed using an Apple IIe software and hardware configuration. This system has demonstrated high efficiency and effectiveness in producing fluent, normal-sounding speech

in adolescents and adults who stutter. Visual feedback from the computer gives the stutterer information about breathing and energy in speech sound production. The program is easily administered with a minimum of training by any qualified speech-language pathologist.

Language Impairments

Ongoing studies are examining the language learning process in preschool children with specific language impairments (that is, childhood language disorders in the face of normal intelligence, hearing, social skills, and neurological status). Studies will determine whether there are optimum times for providing direct treatment. Determining how responsive a child is or the degree to which a child can be stimulated will indicate if treatment will either induce new language skills or accelerate mastery of inconsistent ones. The outcome of this research will shed light on the language acquisition process and provide guidelines for clinical decisions regarding whom to treat and when.

Upper Respiratory Infections

Papillomavirus infections of the larynx and upper respiratory tract cause a serious and potentially life-threatening disease that affects both children and adults and can result in complete respiratory obstruction. Conventional and experimental therapies, including the CO₂ laser chemotherapy, vaccines, and interferon, among others, have failed to cure this disease. Studies are examining the use of photodynamic therapy (PDT) using dihematoporphyrin ether (DHE) in the treatment of recurrent respiratory papillomatosis. This approach has been effective in animal studies, and current research will demonstrate the efficacy and safety of DHE/PDT for the treatment in humans of this debilitating and sometimes fatal disease.

Smell Receptors

Laryngectomized patients experience problems with their sense of smell. The use of a specially designed larynx bypass tube resolves the problem to a significant degree, and additional improvement can be achieved by training the patients to use certain sniffing strategies. Research indicates that the restoration of function appears to be primarily due to the reestablishment of airflow to the olfactory receptors rather than to any sort of larynx-dependent neural network.

Cochlear Implants

The cochlear implant is an electronic device that delivers stimulus to the auditory nerve. Part of the device is implanted in the temporal bone, a wire is imbedded into the cochlear,

and part is worn like a pocket-type hearing aid. The cochlear implant is not a hearing aid. It is most effective with the profoundly deaf who suffer from sensorineural deafness and who are no longer able to understand speech with a hearing aid.

A longitudinal study of children who have received cochlear implants is examining effectiveness of different rehabilitation strategies using the implant device alone or in combination with a tactile communication device. These studies are expected to provide new direction in designing strategies to increase hearing capabilities in deaf children. Because hearing is the primary sense through which children acquire speech and language, this work is particularly important in helping children deafened early in life to use the auditory input provided by the cochlear implant to develop communication skills.

Diuretics and Hearing Loss

Prevention of hearing loss associated with long-term use of loop diuretics is being investigated utilizing substitute drugs. Loop diuretics, such as furosemide, are widely used for treatment of hypertension, kidney disease, and glaucoma. Thus, potentially serious side effects of commonly used drugs might be reduced. This has especially important implications for older Americans, who are the most common users of loop diuretics.

National Institute of Dental Research

Oral Health Care

Research supported by the National Institute of Dental Research (NIDR) is investigating how improved knowledge and actions on the part of oral health care providers can affect the oral health status of patients. Investigators in one project are instructing dental residents and assistants in behavioral skills to reduce fear among poor and minority adult patients. Another project is studying the impact of continuing education for practicing dentists on the periodontal health of patients. These projects should improve use of professionally provided preventive services.

Because maintenance of oral health is dependent on self-care, NIDR encourages research that addresses skill development and compliance. Skill interventions, emphasizing self-efficacy and outcome expectations to improve long-term adherence to self-care among young adults at risk for

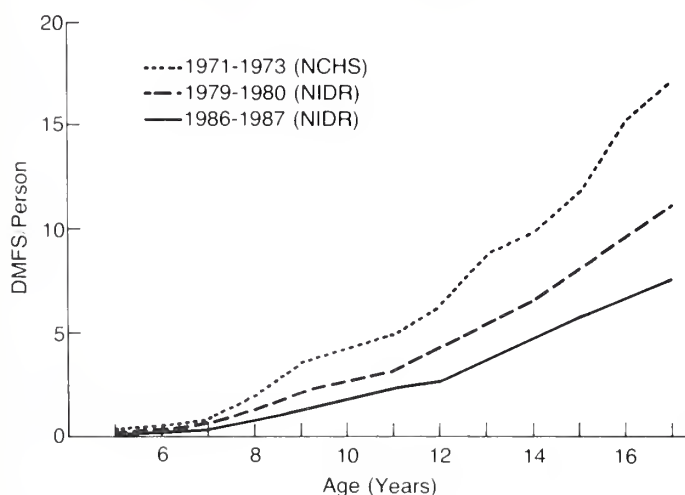
periodontal diseases, are being investigated. In one controlled study, one group is receiving a three-session treatment that includes health education, skills training in plaque removal, and performance feedback. The control group is receiving a less intense intervention. Additional efforts are directed toward fostering the maintenance of regimen behaviors. Measurements are followed for 1 year beyond initiation of treatment.

Social learning theory is being used with adults to improve oral health status. One project is evaluating the provision of prophylaxis, instruction, cognitive behavioral enhancement, self-rating, and rating of model oral health to improve levels of knowledge and oral health status.

Cognitive Counseling

Researchers are studying the impact of cognitive counseling and support groups; use of interactive videodiscs to prepare patients for major dental work; or a media program to reduce fear about treatment. One investigation with head and neck radiation patients is evaluating the impact of a color slide narration and three different fluoride regimens on dental caries and periodontal disease status. In another study with a panel of naval recruits, the association of smokeless tobacco use with dental caries and other oral diseases is being studied using measures of coronal and root caries and plaque, among other outcomes.

AGE-SPECIFIC MEAN DMFS IN THREE NATIONAL EPIDEMIOLOGICAL SURVEYS, U.S.



Oral Health of U.S. School Children. NIDR 1987

Dry Mouth

Specific attempts are being made by NIDR scientists to improve preventive regimens for individuals at high risk for diseases. For example, preventive regimens are being developed for cancer patients at risk for dry mouth (xerostomia) as a result of radiation to the head and neck. Another study is testing a formal orientation program to inform and motivate patients receiving head and neck radiation treatments. The program uses specialized oral health care regimens to compare the preventive effects of three topically applied fluoride regimens on the overall oral health status of these patients.

National Institute of Diabetes and Digestive and Kidney Diseases

Preventing the Early Onset of End-Stage Renal Disease

Each year, thousands of patients who have been afflicted with a variety of chronic disorders of the kidney reach a point in the downhill progression of their disease where they develop clinical symptoms of kidney failure and become uremic. This final, common pathway of progressive renal failure—uremia—is irreversible and ultimately fatal unless the patient enters a program of thrice-weekly dialysis treatments or receives a kidney transplant, provided a suitable organ is available. The two treatment modalities for terminal renal failure, dialysis and transplantation, are both expensive and still far from ideal. Moreover, the quality of life with maintenance dialysis is less than desirable in the long run. Successful use of a considerably less expensive treatment *earlier* in the natural history of the disease could preserve a near-normal existence, is compatible with the *pro tempore* continuation of gainful employment, and prevents for a significant time the development of end-stage renal failure and the need for dialysis therapy. This approach would be an improvement for these patients and of great importance to the governments that must finance the ultimate and very expensive end-stage renal disease (ESRD) treatment.

Past experiments have indicated that, in many cases, a low protein, low-phosphate diet that is strictly followed can be effective in slowing the development of uremia. The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) has initiated a large, controlled, multicenter clinical

trial to determine (1) if dietary therapy (protein and phosphate restriction) can retard the *progression* of chronic renal failure and (2) if dietary protein restriction (if found effective) is nutritionally safe in patients with progressive renal failure. This clinical trial compares the results obtained in populations of patients that receive experimental diets (low-protein, low-phosphorus with or without additional essential amino acid/keto acid analogue supplementation) and a self-selected, nonrestricted, normal diet. This clinical trial, Effect of Dietary Modification on Renal Disease (DMRD), involves 800 patients, is now in its fourth year, and will continue for another 4 years. It is the largest such well-controlled study. Many similar studies have been conducted in the past, both in Europe and the United States, and have yielded strong indications that this dietary intervention can successfully postpone progress of chronic renal disease. Recently, another such study from Australia, involving about 40 patients, showed similar encouraging results. However, only the outcome of a large study like NIDDK's DMRD clinical trial can provide sufficient statistical validity to justify general introduction of dietary intervention into the treatment of patients with chronic renal disease for postponement/prevention of early ESRD.

Preventing the Anemia of Chronic Renal Disease

The hormone erythropoietin (EPO) is essential for the development and maturation of red blood cells. Its absence produces a profound anemia because normal red blood cells survive in the circulation only temporarily (100-120 days), and the body depends on the continued development of fresh red blood cells in the bone marrow. The EPO is synthesized and released into the circulation by the normal kidney. In chronic renal failure, very little active renal tissue survives in the kidney, and thus less EPO is available for the formation of new red blood cells. Classically, patients with chronic renal failure suffer from profound anemia. In the case of patients with ESRD who are surviving on maintenance dialysis (and who have no or practically no functional renal tissue left), the anemia is even more profound, and the resulting weakness, lack of energy, inability to work, and depression are even more pronounced. Many of these patients (up to 75 percent) require blood transfusions.

Previous NIDDK-funded research made possible the synthesis of genetically engineered, recombinant EPO. Recently, once it was shown to be biologically active, the hormone was systematically administered to chronic dialysis patients

where it effectively corrected universal, characteristic anemia. In these recent experiments, seriously depressed red blood cell mass increased substantially, and blood transfusions became unnecessary. Most patients reported a remarkable improvement in the quality of life, ability to work and exercise, a feeling of well-being, appetite, and even sexual potency. In the United States, a clinical trial involving nine hemodialysis centers is ongoing, and results obtained in 700 patients worldwide continue to follow the successful pattern of the initial studies. If positive results continue, this preventive treatment will have a tremendous impact on the roughly 115,000 patients who are now being maintained by dialysis in the United States in terms of their well-being, quality of life, and ability to work. In the future, EPO will be investigated as a possible preventer of anemia of all chronic renal diseases, which characterizes the years preceding dialysis and causes much of the disability of these patients.

National Heart, Lung, and Blood Institute

New Class of Drugs to Lower Blood Cholesterol Levels

The development of a new class of drugs, the HMG CoA reductase inhibitors, first approved by the FDA in 1987, offers the hope of substantial improvement in the ability of physicians to lower blood cholesterol levels. Well-tolerated and effective in nearly all patients who have received it, the HMG CoA reductase inhibitor lovastatin has been reported to produce significant regression of coronary atherosclerotic lesions when administered together with colestipol. Such drugs may extend the usual range of treatment to older people, many of whom have chronic conditions requiring use of drugs that interact poorly with other cholesterol-lowering drugs. The National Heart, Lung, and Blood Institute (NHLBI) recently initiated a 2-year pilot study of HMG CoA reductase inhibitors to determine whether lowering elevated serum cholesterol levels after age 60, by use of these drugs, will reduce mortality due to atherosclerotic cardiovascular disease.

Estrogen Replacement Therapy and Cardiovascular Disease

Before menopause, women experience a relative freedom from susceptibility to coronary heart disease (CHD) that is thought to be attributable to the protective effects of natural

estrogen. This observation has led to much interest in estrogen replacement therapy to prevent CHD in postmenopausal women. The NHLBI supports a number of studies on the effects of supplemental estrogen on cardiovascular morbidity and mortality, both in women and in non-human female primates.

In 1987, a major clinical trial, the Postmenopausal Estrogen/Progestin Interventions (PEPI) was initiated to assess the effects of various postmenopausal estrogen and progestin therapies on selected cardiovascular risk factors. The results of this trial are expected to provide important new information for recommendations to health professionals and women regarding the use of these preparations.

Asthma

Asthma is a serious chronic disease, affecting approximately 10 million people in the United States, 3 million of whom are under the age of 18. Blacks are twice as likely as whites to be hospitalized for asthma and three times as likely to die from asthma. Asthmatic patients must learn appropriate ways to manage the disease, avoid triggers of attacks, and alleviate symptoms. Since the mid-1970's, behavioral research has addressed ways of teaching asthmatics and their families to manage the disease. Several studies have confirmed that asthma education results in decreases in the number of attacks, better adherence to medication, decreases in days lost from school and visits to the emergency room, and improved school grades. Few of the programs developed thus far are aimed at minority populations. In 1989, NHLBI initiated a research program on Control of Asthma in Black and Hispanic Children to develop model, replicable programs that reduce the morbidity associated with asthma, decrease inappropriate use of health care resources, and enhance the quality of life of asthmatics. Results from these research studies should be useful in public health programs to reduce the gap in asthma morbidity and mortality between minorities and nonminorities.

Cystic Fibrosis

Over the past several decades, improved treatment for cystic fibrosis patients has resulted in increasing numbers of patients living into adulthood. Patients with cystic fibrosis must learn to take appropriate action to manage their condition at home, prevent unnecessary complications, learn to live independently as they grow older, and cope with having a chronic disease. The NHLBI currently is supporting several demonstration and education research projects to assist

patients in managing their disease in collaboration with their physicians. In these educational projects, patients and their families are learning self-management skills, exercise conditioning, medication management, and stress management. These interventions are being evaluated in relation to their effect on the physical health and emotional well-being of the patient.

The Physician's Health Study

Results of an ongoing study suggest that tens of thousands of nonfatal heart attacks can be prevented. The Physician's Health Study is a randomized, double-blind, placebo-controlled trial of alternate-day consumption of aspirin or placebo and beta-carotene or placebo. The primary variables under study are cardiovascular mortality (aspirin) and cancer incidence (beta-carotene) among the participants (22,071 males, U.S. physicians, 40 to 84 years of age in 1982, with no history of heart disease, stroke, or cancer at entry into the study). Although the Physician's Health Study is continuing through FY 1990, the aspirin component was stopped early as a result of persuasive evidence that aspirin reduces the incidence of myocardial infarction, as well as a very low probability that any answer on cardiovascular mortality would be forthcoming, due to lower than anticipated mortality rate. There was a trend, though not statistically significant, for increased stroke, particularly hemorrhagic stroke, in the aspirin-treated group. As a result of this study, aspirin may be prescribed, with appropriate precautions, for several million men at high risk of developing coronary heart disease.

The Cardiac Arrhythmia Suppression Trial

The Cardiac Arrhythmia Suppression Trial (CAST) was designed to evaluate the potential effectiveness of three antiarrhythmic drugs in preventing sudden death in heart attack survivors who had mildly irregular heart rhythms. In April 1989, use of two of the drugs, encainide and flecainide, was halted when it became apparent that death occurred almost twice as frequently among patients who took the drugs as among those who took a placebo. Physicians were immediately advised that these drugs should be used only in patients with life-threatening arrhythmias and not in the cases of mild arrhythmias for which the drugs had been widely prescribed. This experience underscores the importance of the clinical trial as a research tool in evaluating therapeutic applications.

Primary Prevention of Hypertension by Nutritional-Hygienic Means

There is much evidence that dietary and lifestyle factors are associated with the chronic and progressive increase in blood pressure with age that is commonly observed in populations of industrialized countries. Further, a number of studies have demonstrated the efficacy of nonpharmacologic interventions in reducing blood pressure in hypertensive persons. These observations have led to an interest in the possibility that nonpharmacologic interventions may be effective in the primary prevention of hypertension. Recent findings from a trial of 201 subjects with high-normal diastolic blood pressure indicate that even a moderate reduction in risk factors for hypertension contributes to the primary prevention of the disease in hypertension-prone individuals. Study subjects who received individualized intervention to correct being overweight, reduce sodium intake, and improve fitness had less than half the incidence of hypertension of control subjects over a 5-year period. The multicenter Trials of Hypertension Prevention are now under way to assess the effectiveness of various nutritional-behavioral interventions on the development of high blood pressure.

National Institute of Neurological Disorders and Stroke

Neural Tube Disorders and Vitamins

The possible relationship between dietary deficiencies and neural tube defects, such as spina bifida, is of longstanding interest. In the past few years, several studies have offered conflicting evidence on the protective effect of dietary or supplemental folate in reducing the risk of neural tube defects. Recently, a new study involving more than 20,000 pregnant women indicated that the prevalence of neural tube defects among women who used folic acid-containing multivitamins during the first 6 weeks of pregnancy was substantially lower than that among those who did not consume supplements. These studies are stimulating questions about the mechanistic role of folate and other nutrients in neural tube formation and genetic and metabolic differences in the utilization of nutrients among pregnant women and their offspring. They also are pointing to the need for more refined studies examining possible relationships between specific types of neural tube defects and various environmental exposures, including nutrient intakes.

Medical Treatment to Prevent Stroke in People With Atrial Fibrillation

Stroke ranks as the third leading cause of death in the United States. Medical and nursing care, physical therapy, lost income, and other expenses due to stroke cost the Nation an estimated \$11.3 billion annually.

The National Institute of Neurological Disorders and Stroke (NINDS) scientists and grantees have been actively studying the feasibility of using anticlotting drugs to prevent stroke. Basic and animal research studies have suggested several potential agents. The NINDS Stroke Prevention in Atrial Fibrillation (SPAF) study was launched to evaluate the effectiveness of two of these agents—aspirin and warfarin. Preliminary results from the study revealed that both drugs were so beneficial that the risk of stroke was cut by 50 to 80 percent. The magnitude of the protective effect spurred the investigators to drop the placebo portion of the study and provide active treatment to all patients. Further studies are needed to determine long-term effects from treatment and to determine the relative benefits of warfarin compared with aspirin. However, the results obtained so far suggest that 20,000 to 30,000 strokes can be prevented each year with proper treatment. The resulting savings from health care costs and continued productivity will be in the millions.

National Center for Nursing Research

Infant Health

Alleviating the consequences of prematurity and other conditions that contribute to infant morbidity and mortality is a national priority. The National Center for Nursing Research (NCNR) is supporting studies to examine therapeutic behaviors used in caring for preterm infants and measuring outcomes from these behaviors. Other infant health problems being studied include profound deafness, irritable infant syndrome (colic), and developmental delays. The impact of these conditions on parent-child relationships is being analyzed to determine parent coping strategies.

Health in Pregnancy

Events surrounding pregnancy and childbirth affect the health of mothers and children. The NCNR investigators are examining interventions that affect recovery from cesarean section as well as support for women who miscarry and for those afflicted with postpartum depression. One researcher

is studying the effects of both psychosocial factors, such as life stress and social support, and biochemical factors, such as thyroid dysfunction, on postpartum depression symptoms. Anticipated results from these areas of research will provide information that can be used to assist mothers during pregnancy and childbirth.

Promoting Maximum Potential for Growth and Development

Parenting that provides for the growth and development of children ensures healthy generations in the future. Several studies are identifying interventions for improving parenting skills. For example, investigators are examining the effects of parental behaviors and attitudes, the characteristics of infants, and the correlations between these factors. Families from various ethnic backgrounds and socioeconomic levels are the subjects of projects focused on identifying cultural factors that affect parenting.

Behaviors That Promote Health

Because changes in lifestyle are an important factor in lowering the incidence of many diseases, positive health-related behaviors need to be identified and reinforced. Studies funded by NCNR have identified adult populations at risk for disease such as smokers, those at risk for breast cancer, battered spouses, bereaved spouses, and individuals recovering from coronary disease or hip fractures. Research is examining ways to assist these groups with improving their self-care and preventing further complications. Two studies are analyzing learned health-related behaviors in adolescents to identify factors that influence their choices of health risk behaviors such as drug use, smoking, and early sexual activity. These studies will enhance the existing knowledge base for the development of interventions and clarify strategies that can prevent illness and promote the health of the Nation.

***T**here are a number of NIH programs relevant to prevention that feature interactions with the scientific and public health community, health providers, and consumers. The following describe selected educational activities.*

National Institute on Aging

Alzheimer's Disease Education and Referral Center

As directed by the Omnibus Health Bill, P.L. 99-660, the National Institute on Aging (NIA) awarded during FY 1990 a contract to establish a national Alzheimer's Disease Education and Referral (ADEAR) Center to gather, maintain, and disseminate information on Alzheimer's disease research and services.

The ADEAR distributes information about Alzheimer's disease to health professionals, patients and their families, and the general public. The center also will develop materials in a variety of media to support health education campaigns.

National Institute of Allergy and Infectious Diseases

Asthma

Several of the Centers for Interdisciplinary Research on Immunologic Diseases (CIRID) have outreach and demonstration and education research components concerned with self-management of asthma. The goal of these projects is to determine the best methods to educate particular patient groups because educated patients and their families can enter into a partnership with health care providers that results in optimal care. This, in turn, reduces morbidity and mortality, reduces absenteeism from school, and improves the quality of life for patients and their families. The patient groups in these studies include urban minority (black and Latino) children and teenagers.

AIDS Outreach and Technology Transfer Program

The National Institute of Allergy and Infectious Diseases (NIAID) provides health care workers with the latest information on AIDS through an outreach and technology transfer program based in the Office of the Director, NIAID. Since 1983, more than two dozen conferences, workshops, and symposia have been organized by NIAID, in cooperation with local agencies, universities, hospitals, and state and city health departments, in cities across the country and in Puerto Rico.

Participants in the meetings have included physicians, registered nurses, practical nurses, infection control nurses, medical technologists, dentists, dental hygienists, laboratory technicians, social workers, drug counselors, policy officers, firefighters, morticians, and other service and support personnel.

The conferences present information on the epidemiology of AIDS, research efforts in treatment and vaccine development, patient management, and ethical, legal, and psychosocial issues of particular concern to those who care for persons with AIDS. In collaboration with various professional health organizations, NIAID also has conducted or supported conferences on specific aspects of AIDS, such as AIDS in children, and has sponsored workshops on AIDS at national and regional professional meetings of nurses, social workers, physicians, and minority health care workers.

National Institute of Arthritis and Musculoskeletal and Skin Diseases

Sunlight, Ultraviolet Radiation, and the Skin

Exposure to natural or artificial ultraviolet radiation has the potential for causing acute and chronic adverse effects on the skin. Expanded knowledge about the hazards of ultraviolet

radiation has been accompanied by improved approaches to photoprotection. Preliminary evidence suggests that it may be possible to inhibit or reverse certain chronic effects of sun exposure.

In 1989, the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) cosponsored an NIH consensus development conference to define the specific interaction of ultraviolet radiation and the skin and to identify methods to prevent and/or treat the adverse effects of ultraviolet radiation. A number of preventive steps were identified that people can take to reduce the risk of ultraviolet radiation damage.

- Clothing made of tightly woven fabrics with long sleeves and long pants will provide some protection against ultraviolet radiation.
- Maximum protection can be obtained by using sunscreens with a sun protection factor of at least 15.
- Combination sunscreens that are effective against the spectrum of solar wavelengths are preferable. Daily use is recommended as appropriate, throughout the year.

National Cancer Institute

Cancer Prevention Awareness Program

Since 1984, the National Cancer Institute (NCI) has conducted the Cancer Prevention Awareness Program, a major effort to increase public awareness of the possibilities for cancer prevention. It challenges the American people to learn what they can do on a daily basis to control their cancer risks. The program offers specific information for individual action based on the most recent scientific information related to cancer and prevention.

The general prevention awareness program relies on mass media and the Cancer Information Service (CIS) as primary avenues for the dissemination of its messages. Activities have included development of electronic and print media messages, distribution of printed materials, promotion of the toll-free CIS number 1-800-4-CANCER, and development of Partners In Prevention, a network of some 2,000 individuals and organizations involved in community-based prevention activities.

In addition to the overall public awareness component of the program, intensified program efforts currently focus on two risk factors, tobacco and nutrition, and on one population

group, black Americans, because these areas offer the greatest potential for reducing cancer risk and influencing the cancer death rate.

The Working Guidelines for Early Cancer Detection developed in collaboration with national medical organizations have been adopted by the National Cancer Advisory Board and by most of the collaborating organizations and societies. For the first time, nearly universal agreement has been reached on controversial cancer detection issues, thus promoting more consistent messages on this subject to practicing physicians. Guidelines have been developed for seven cancer sites based on the best available evidence and clinical judgment.

In a direct approach to reducing cancer death rates, NCI makes state-of-the-art information about cancer available through a national information system established in 1976. Anyone in the United States can reach the CIS at its toll-free 1-800-4-CANCER number. The CIS also has access to NCI's Physician Data Query (PDQ), which lists state-of-the-art treatment and clinical trials throughout the United States.

The NCI's PDQ contains up-to-date information on the prognosis, histopathological classification, staging, and treatment for all major tumors. Summaries of all active investigational studies supported by NCI are in PDQ along with additional studies not supported by NCI that have been submitted by clinical investigators. The PDQ also contains a directory of physicians and organizations that provide cancer care. Recently, protocols and investigators from the European Organization for Research and Treatment of Cancer (EORTC) were added to the database.

Tobacco Education

Information and education activities in the tobacco education program are targeted to two groups: the general public, to increase awareness of the risks of tobacco use and to encourage cessation among users; and health professionals, to enhance their involvement and skills in counseling patients about smoking cessation and cancer prevention. Special efforts are being made to package and disseminate the results of NCI-supported tobacco intervention research in practical how-to manuals for health professionals, educators, media advocates, and other tobacco control activists.

One project, a special communications initiative, was developed to assist the District of Columbia Health Department in developing and implementing an effective cancer

prevention and control plan for the city. Antismoking public service announcements featuring the Washington Bullets' basketball coach were developed, and the approaches developed in the District of Columbia will be applied to black communities throughout the Nation. The NCI staff members also are working with supermarkets in minority areas to expand NCI's previous cooperative effort with a supermarket chain to develop and test in-store education programs to help cut the risk of cancer.

Nutrition

The focus of the nutrition education program is on increasing awareness in the general population of the link between diet and cancer and on providing clear, practical advice about changes individuals can make in their diets to increase fiber and reduce fat intake. Special efforts are being made to develop strategies and materials for a nationwide supermarket education program, particularly in regions serving large minority, low-income, and blue-collar populations.

Prevention Awareness for Black Americans

The prevention awareness program for black Americans capitalizes on institutions and networks that reach black audiences in both urban and rural areas. The NCI also is supporting community-based cancer prevention activities through five master agreement projects in New York, Philadelphia, Houston, Detroit, and the State of Illinois. Similar activities are being planned and conducted to reach Hispanic Americans with cancer prevention information and to reduce fear and fatalism associated with cancer in this population.

Breast Cancer Screening

Breast cancer will claim some 44,000 lives in 1990, but that figure can be cut by more than 30 percent with effective screening. In October 1989, a nationwide breast cancer screening education program was launched at the Women's Leadership Summit on Mammography, an event cosponsored by NCI and the Susan G. Komen Foundation. In addition, a cooperative network of intervention studies to improve use of mammography, breast exams, and breast self-examination is under way in seven states: California, Massachusetts, New Jersey, New York, North Carolina, Pennsylvania, and Washington.

The NCI is working to inform professionals of recently established consensus guidelines on mammography and to encourage them to refer women 40 and older for routine screening mammograms. The NCI also is mounting a public

education campaign for women to inform them about the importance of mammography, dispel misconceptions about the procedure, and encourage actual use of mammography. Key communication channels include the mass media and organizations with large constituencies of women older than 50.

National Institute of Dental Research

Oral Health Information

The National Institute of Dental Research (NIDR) conducts a comprehensive information program to ensure that research advances in oral health are shared with the public and with health professionals in a timely manner. Patient and professional education materials, publications, exhibits, scientific reports, and films are being used and are updated as necessary. Also, NIDR has extensive contacts with the trade and general broadcast media, including professional and lay journals and magazines. A film on periodontal diseases recently has been updated, and revisions of pamphlets on dental sealants and baby bottle tooth decay are being made.

Fluorides and Oral Health

The NIDR continues to promote the use of fluorides in school-based programs, especially in fluoride deficient communities, and efforts recently have been made to promote the application of sealants in specific age groups related to the time that permanent teeth usually erupt.

The NIDR continues to review the state of the science of preventive strategies as part of its science transfer activities. A symposium was sponsored in Georgia to review mechanisms of action and recommendations on use of fluorides, and NIDR supported a Centers for Disease Control workshop in Michigan on the public health implications of fluorides. Other projects involving efficacy of fluorides and medical benefits include the impact on osteoporosis of lifelong residence in fluoridated communities.

Oral Health and Cancer

The NIDR has been working with NCI to develop an educational training program on tobacco cessation techniques for dentists and dental hygienists. The materials were developed as an adaptation of materials used with physicians and have been tested for a broad-based training program.

Infection Control

The Institute has been collaborating with other organizations and agencies to improve the knowledge of dental health care providers regarding infection control practices. A three-part audiovisual education program was developed and distributed to dental schools, other training facilities, and health departments throughout the Nation.

Year 2000 Health Objectives

Major NIDR prevention activities this year have been the provision of staff support for the development of the year 2000 national health objectives; the background paper for the Surgeon General's Workshop on Health Promotion and Aging; and the oral health issue paper for an Institute of Medicine report, "Disease and Disability Prevention for the Second Fifty."

National Institute of Diabetes and Digestive and Kidney Diseases

Professional and Public Education

There are a number of National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) programs that are relevant to prevention and that feature interaction with the scientific and public health community, health providers, and consumers. The following describe the most important of these educational activities.

- *Diabetes Research and Training Centers.* These centers have education and demonstration components with information, continuing education, and training programs for medical and allied health professionals and for patients. Of particular importance are education and dissemination of information for the general public concerning risk factors associated with disease, the importance of early diagnosis and treatment, and discouragement of use of unapproved and ineffective treatment measures.
- *Epidemiology, Data Systems, and Diabetes Data Group.* These efforts encourage epidemiologic research that may provide leads to causative factors in the various diseases under NIDDK purview, develop bases for prevention programs through risk factor modification, and assess the effectiveness of preventive regimens through clinical studies. The Diabetes Group coor-

dinates the collection of data from multiple sources, makes them available to a variety of users, and serves as a central source for accurate statistics—all essential to development of preventive public health programs.

- *Clearinghouses and Office of Health Research Reports.* The NIDDK supports national information clearinghouses on diabetes, digestive diseases, and kidney and urological diseases. These serve the information/education needs of a broad professional and lay constituency in a number of areas, including disease prevention and health promotion. They act as central resources for information on scientific and popular literature and produce specialized newsletters, bulletins, and other publications. Similarly, NIDDK's Office of Health Research Reports acts as a central resource for all of NIDDK's research programs and categorical disease areas, especially through production and dissemination of information brochures for the lay public and through its active information service to science writers and major public communications media.
- *Clinical Nutrition Research Units.* Supported by NIDDK at selected medical schools, Clinical Nutrition Research Units are designed to: strengthen multidisciplinary research in clinical nutrition; improve education and training of medical students, house staff, hospital-associated practicing physicians, and paramedical personnel in clinical nutrition; and enhance improved patient care through better institutional support services. These innovative programs encourage the principles of disease prevention and health promotion by striving to upgrade the use of nutrition knowledge in clinical practice.
- *Special Activities.* This includes regularly scheduled events like the Institute's Annual Diabetes Day—a postgraduate seminar for practicing physicians organized and presented by NIDDK's intramural staff. On an ad hoc basis, the Institute organizes NIH consensus development conferences with a prevention focus (such as osteoporosis, health implications of obesity, and prevention and treatment of kidney stones) or cosponsors with the respective National Advisory Board a prevention-related conference on a particular disease.

National Institute of Environmental Health Sciences

Alaskan Oil Spill—Long-Range Effects on Human Health

Scientists at the National Institute of Environmental Health Sciences (NIEHS) sponsored the first major symposium to discuss potential human effects resulting from the Exxon Valdez tanker oil spill into Prince William Sound. The effects of the oil spill on marine mammals, commercial fishing, and other animals were described in detail in the news media. But risks to humans were not given much public attention. Cleanup workers who labored for days at a time in the same oil-soaked clothes, literally up to their elbows in crude oil, were of particular concern to the participants in the NIEHS symposium.

Crude oil contains polycyclic aromatic hydrocarbons and volatile organic components such as benzene, a known human carcinogen. Skin contact with crude oil can cause acute dermatitis. Examination of dead otters taken from Prince William Sound revealed severe emphysema—presumably from breathing the fumes of the freshly spilled oil—as well as liver, kidney, intestinal, adrenal, and bone marrow abnormalities, similar to damage previously found in studies of laboratory rats. Fortunately, the highly toxic components—the polycyclic aromatic compounds—evaporated from the spilled oil within several days. Once the aromatic compounds are gone, crude oil has a relatively low carcinogenic potential.

However, oil components may be present at dangerous levels in fish and shellfish harvested from fouled waters by native subsistence fishermen. This may put the natives, who rely on seafood for 80 percent of the protein in their diets, at increased risk of cancer or other organ damage. Commercial fishing in oil-contaminated waters has been banned by the Food and Drug Administration, but natives may catch fish in contaminated waters, which, unlike commercially caught fish, is not inspected.

No one knows for sure how serious the risk is because little funding is available to study the subsistence catch. The Prince William Sound Extended Studies Program undertaken by the National Oceanic and Atmospheric Administration (NOAA) with advice from Federal agencies, including NIEHS, is supposed to take maximum advantage of the spill by documenting ecological recovery and the cultural and

social effects of the spill and to evaluate the cleanup operation. So far, NOAA has found contamination in mussels and pink salmon. However, these tests were not adequate to estimate the full extent of contamination to other fish and wildlife. It seems clear, nevertheless, that a potential human health risk has been identified.

The NIEHS believes biomarkers for crude oil exposure must be identified and more laboratory studies conducted. The Institute is considering sponsoring a workshop to review data collected and recommend how to plan better for future responses to oil spills.

National Eye Institute

National Eye Health Education Program

Although the National Eye Institute (NEI) has been committed to communicating the results of completed research, large-scale health education programs until recently have been limited by a lack of funding and manpower. However, beginning in FY 1988, the U.S. Congress appropriated funds for NEI to “increase its commitment to the prevention of blindness through public and professional education programs and the encouragement of regular eye examinations.” With this congressional mandate and a designated appropriation, NEI has established the National Eye Health Education Program (NEHEP) as the vehicle for large-scale information, education, and applied research programs. The initial emphasis of the NEHEP is on public, patient, and professional education concerning the importance of early detection and treatment of diabetic retinopathy and glaucoma.

An NEHEP planning conference was held in March 1989 with 65 participants from 38 professional, voluntary, civic, government, and private organizations attending its plenary sessions, workshops, and exhibits. The plenary sessions addressed the science base of the NEHEP, the health communication process, and examples of ongoing health education programs. Workshops on glaucoma and diabetic retinopathy helped to define these audiences and their information and education needs and to propose strategies for reaching these target audiences. A strategic plan is under development and will include specific recommendations for NEHEP activities for each target audience identified at the planning conference.

National Heart, Lung, and Blood Institute

Models for Public Screening for High Blood Cholesterol

As an adjunct to the National Cholesterol Education Program (NCEP), the National Heart, Lung, and Blood Institute (NHLBI) supports several applied research programs. Through this demonstration and education research, the logistical and practical implications of implementing the NCEP recommendations are being addressed. For example, models for public screening for high blood cholesterol and primary care models for treating the condition are being developed. Public screenings for cholesterol have increased rapidly in response to public education efforts and with the availability of portable chemical analysis equipment for measuring blood cholesterol. Problems with public screening, such as reliability of the portable analyzers and patient compliance with referral advice, have been the focus of this research. Based on these studies, guidelines for conducting public screenings are being widely disseminated in an effort to ensure high-quality screening.

Academic Award in Systemic and Pulmonary Vascular Disease

This proposed academic award will address problems that prevent the effective application of new developments in diagnosis and care to the individual patient with vascular disease. The rapid advance of basic and clinical research and the absence of a specific specialty dedicated to such patients have impeded the efficient transfer of new technology to patients with vascular disease. These awards will have the dual purpose of encouraging the development and/or improvement of the quality of the clinical, educational, and research programs in vascular disease and encouraging the professional development of the awardee so that he or she can serve as the focal point for multidisciplinary interactions in the field of vascular medicine. The award is expected to strengthen the diagnostic, therapeutic, and preventive approaches to these diseases.

Preventive Pulmonary Academic Award

Advances in the prevention of disease and disability have made major contributions to improving the health of Americans. Yet patient cooperation with medical treatment plans remains generally low. And although the medical community recognizes the importance of preventing disease and

promoting health, comprehensive prevention programs have not been widely integrated into medical school curricula throughout the country. Respiratory disorders in particular are major causes of morbidity and mortality, but the potential for preventing or ameliorating lung disease is great. The NHLBI currently supports a program to develop and improve the teaching of respiratory disease prevention in medical schools and to promote research in preventing pulmonary diseases. Awardees in this program are working in medical schools to include prevention of respiratory diseases in the curriculum and to teach medical students, fellows, and house staff about prevention activities such as preventing severe and life-threatening episodes of asthma, helping patients to quit smoking, promoting the use of influenza vaccinations, and preventing occupational lung diseases.

National High Blood Pressure Education Program

Begun in 1972, the National High Blood Pressure Education Program is the first and oldest of NHLBI's five major education programs. The program, made up of medical, public health, and voluntary organizations, operates as a partnership between the public and private sectors. High blood pressure is the major cause of stroke, and since 1972, the mortality rate for stroke declined by more than 50 percent. Since 1972, physician visits for hypertension increased by more than 73 percent while the increase in physician visits for other causes was only 7 percent. The proportion of hypertensives who are controlling their blood pressure also has increased. By 1985, 77 percent of the public knew that high blood pressure increased a person's chances of having a stroke, and 91 percent reported that high blood pressure increases a person's chances of getting heart disease. The program continues to provide education messages for the public, including an annual mass media public service advertising campaign. The program issued an updated report on therapy recommendations that received wide dissemination to health care professionals in FY 1989. A major effort in FY 1990 will be a special initiative to reduce stroke in 11 southeastern states that form the "Stroke Belt," a region having a higher stroke mortality rate than the rest of the country.

National Cholesterol Education Program

The NCEP was launched in 1985, based on the findings of the Coronary Primary Prevention Trial (January 1984) and the recommendations of the NIH consensus development conference panel on lowering elevated blood cholesterol

(December 1984). The program's coordinating committee comprises more than 25 national medical, public health, and voluntary organizations, which have joined in a national effort aimed at lowering elevated blood cholesterol in the United States. An expert panel was convened to develop detailed, comprehensive recommendations for the proper treatment of high blood cholesterol. Its report (released October 1987) on how to detect, evaluate, and treat patients with elevated blood cholesterol represents a major step in getting approximately 40 million Americans under appropriate diet and/or drug therapy. Another panel was convened to address the problem of laboratory standardization as a means of enhancing the accuracy and reliability of blood cholesterol measurements. Several physician education efforts have been launched by the program or by others collaborating with the program, and a mass media campaign urging the public to "know your cholesterol" is now under way. Drawing on the high blood pressure model, the program develops partnerships and networks of public and private sector groups to carry educational messages to professional and public audiences and to stimulate activity that would improve detection and treatment of high blood cholesterol. The program recently released a major report on population-based approaches to changing dietary patterns. Another report on detection and treatment of high blood cholesterol in children and adolescents is anticipated for release in 1991.

Smoking Education Program

The NHLBI conducts a targeted program on smoking and heart and lung disease, focusing on issues not covered by other Public Health Service agencies. The program has developed motivational messages and educational tools to aid busy physicians and other health professionals in smoking intervention efforts. One of the major themes is to take advantage of a clinical opportunity when the patient may be most susceptible to smoking cessation attempts. A series of print and audiovisual tools supporting this theme has been produced to stimulate more physician interest and involvement in patient education. These materials are being used in self-instructional, continuing medical education, and inservice training opportunities to help physicians. In addition, a comprehensive guidebook was produced for respiratory care therapists to help them intervene effectively with their patients who smoke. The program will continue to work with major public and private sector agencies to assess and disseminate these tools and develop new initiatives. A recent effort, for example, involved a cooperative project with the

Office on Smoking and Health, Centers for Disease Control, to develop television public service announcements and print materials on smoking relapse and heart disease. Plans for FY 1990 include a similar cooperative venture aimed at older smokers.

National Asthma Education Program

The NHLBI's efforts in asthma education initially focused on development of four programs for teaching childhood asthma management skills. The programs were based on NHLBI-funded research and packaged by NHLBI for dissemination. Special efforts have been made to stimulate use of the materials by key professional groups that care for pediatric patients with asthma. In recognition of the growing prevalence and increasing mortality of asthma in the United States, NHLBI launched the National Asthma Education Program in 1989. Modeled after the National High Blood Pressure Education Program, the asthma program operates as a partnership with voluntary, professional, and community organizations concerned with asthma treatment and control. It will carry out broad programs of patient and professional education, especially aimed at minority populations. In 1990, the report of an expert panel will provide recommendations on comprehensive asthma diagnosis, treatment, and management for physicians and other health professionals.

Physician's Survey on the Prevention of Lung Disease

The NHLBI recently completed a national survey of pulmonologists, allergists, family practitioners, and specialists in occupational medicine to determine current practices to prevent lung disease. Results of this survey provide a basis on which to develop future educational programs for physicians and other health care professionals to enhance prevention of pulmonary disease in this country.

National Blood Resource Education Program

In October 1987, the National Blood Resource Education Program (NBREP) was formally launched. The NBREP established a coordinating committee, representing more than 20 national organizations, to address priority issues and determine future program activities. The program's goal is to ensure an adequate and safe supply of blood and ensure the appropriate transfusion of blood and blood components. Educational messages are directed at influencing the awareness, knowledge, attitudes, and behavior of health professionals, patients, and the general public. In FY 1989, the program released two major reports providing guidance for

health professionals—one on the use of red blood cells, platelets, and fresh frozen plasma and the other on the use of autologous blood. In addition, a mass media public education program was begun to supplement the efforts of local blood centers in recruiting blood donors. In FY 1990, an important program focus will be the production of a resource kit to help blood bank personnel improve donor recruitment and retention.

Early Warning Signs of Heart Attack

In FY 1990, NHLBI will conduct a needs assessment and planning effort for a secondary prevention program on early warning signs of heart attack. The program would be aimed at reducing damage to the heart by decreasing the time interval between the onset of heart attack and admission to an intensive care setting. The program would be based on the growing consensus that existing thrombolytic agents offer lifesaving potential to millions of Americans who will suffer heart attacks in the next few years. In early FY 1991, NHLBI will sponsor a conference to explore various issues related to an early warning signs educational effort, including the state of the research, cost and public health implications, impact on the medical emergency system, and other concerns.

Fogarty International Center

Liver Cancer Prevention

An International Workshop on Pathogenesis and Prevention of Hepatocellular Carcinoma (HCC) was held February 13-15, 1989, in Hawaii. It was cosponsored by the International Studies Program of the Fogarty International Center (FIC) and NCI in cooperation with the Cancer Institute of the Chinese Academy of Medical Sciences (CAMS) and Merck and Company. The importance of liver cancer as a major worldwide human malignancy was stressed, along with the etiologic role of chronic transmission of hepatitis B virus (HBV).

It is generally agreed that HCC is a result of HBV infection during early life. HBV vaccine theoretically should prevent subsequent HCC development.

The recent lowering of the cost of hepatitis B vaccines has made it possible to initiate a global HBV immunization program for newborns at risk of vertical HBV transmission. How effective the vaccine will be in preventing HCC development remains to be established.

The workshop considered prevention strategies for HBV carriers at risk of developing HCC. This further facilitated the cooperative efforts between NCI and CAMS to conduct long-term controlled studies to evaluate the efficacy of HBV vaccine against future HCC development. It is expected that a unique research situation exists in rural China, where both HBV and HCC are prevalent. This research will contribute greatly to the needed information in this field. Discussions took place concerning how best to implement the needed HBV vaccine studies in China and other areas of the world. As the result of this workshop, NCI announced a request for research applications to stimulate research toward liver cancer prevention.

New Tuberculosis (TB) and Leprosy Vaccine

Subsequent to FIC's International Workshop on Research Towards Global Control and Prevention of Tuberculosis With an Emphasis on Vaccine Development (November 1987), a workshop participant reported the development of a vaccine with promise for triggering an immune response against tuberculosis and leprosy. Following additional animal studies, clinical trials may begin within 2 years. Each year, 10 million new cases of TB occur globally resulting in an estimated 3 million deaths. In the United States, approximately 22,000 new cases are reported, and 2,000 victims die annually. As for leprosy, this vaccine, if proven safe and effective, may have an impact on 11 million people worldwide, primarily in Asia, Africa, and Latin America.

Professional and Public AIDS Research and Training

The FIC collaborated with NIAID to establish an International Network for AIDS Research and Training. The network links the major international AIDS programs of the NIH, the Centers for Disease Control, the U.S. Agency for International Development, the World Health Organization, the Global Programme on AIDS, and the Pan American Health Organization. The network facilitates the coordination of research and research training needs and the formation of collective strategies to respond to emerging and unanticipated events as the AIDS epidemic progresses. Cooperation through the network also minimizes duplication of effort not only between the FIC and other NIH grantees but also between U.S. and other governmental and international organizations.

1989 NIH Prevention Research Dollars and Personnel

Institute	Prevention Research Dollars (in thousands)	Prevention Personnel FTE's (full-time equivalents)
NCI	481,687	812
NHLBI	179,510	189
NIDR	27,937	102
NIDDK	124,200	120
NINCDS	49,228	169
NIAID	134,167	171
NIGMS	3,962	1
NICHD	181,895	169
NEI	48,648	50
NIEHS	187,184	558
NIA	131,996	64
NIAMS	72,167	63
NIDCD	18,879	0.5
NCRR	60,325	0
NCNR	5,447	3
FIC	—	5
Total	1,707,232	2,476.5

NIH Disease Prevention Seminar Series

***T**he NIH Disease Prevention Seminar Series is sponsored by the NIH Prevention Coordinators Committee and the Office of Disease Prevention. This seminar series is designed to present the findings of scientific research that may be both useful and interesting to NIH employees and the scientific community. Speakers for each seminar are selected for expertise and knowledge in their field.*

The following abstracts were prepared by the presenters for the 1990 Seminar Series.

NIH Disease Prevention Seminar Series Abstracts

Prevention of Stroke in Rochester, Minnesota

Jack P. Whisnant, M.D.

Chairman, Department of Health Sciences Research, Mayo Foundation

Professor of Neurology, Mayo Medical School

Presented on January 5, 1990

We must first consider how the judgment is made concerning what is having an effect on the occurrence of stroke.

Relative Risk

This is the probability of stroke for a part of the population that is exposed to a risk compared with the probabilities of stroke in the unexposed population. This is expressed as a ratio. For example, a relative risk of 5 is a risk that is 5 times greater in the exposed than in the unexposed population.

Prevalence

This takes into consideration how common the risk is in the whole population and is simply the proportion of the particular population that has the risk factor present.

From these two we can estimate the proportion of stroke in the population that can be attributed to the risk under consideration. This is estimated by the following formula:

Population Attributable Risk (PAR) % =

$$\frac{P(R-1)}{P(R-1)+1} \times 100 \quad P = RR$$

P = prevalence, R = relative risk, and 1 is the risk in the unexposed population.

We should also consider how long a risk has been present to influence the occurrence of stroke and what the effect of management or correction of a risk is on the occurrence of stroke.

We have used the resources of the Rochester Epidemiological Project, which includes the record system of the Mayo Clinic and a record linkage system, linking all other medical care facilities in Olmsted County, Minnesota, with the Mayo Clinic record system in a single computer file for indexing and retrieval.

Using these resources, we established a cohort of more than 1,800 persons over the age of 50 years in 1960 who had a general exam and had not had a prior stroke or transient ischemic attack. This cohort was observed for 13 years through the medical record during which time the average individual had 19 medical evaluations. Eighteen potential risk factors were considered in a time-dependent covariate analysis for ischemic stroke. The time-dependent covariate analysis uses the Cox proportional hazards model, judging each risk factor as it appears and as it attributes person-years of observation before stroke. Those factors that had an independently significant relative risk are noted in the table.

To provide a benchmark for estimates of prevalence of factors that are associated with an increased risk of stroke, we did a cross-sectional survey of a 10 percent sample of the Rochester population over the age of 35 years, selecting the households through a random digit dialing technique. When various potential risks were identified from an interview, we then used the medical record to confirm or reject the presence of a particular risk factor in the individual person. The ability to confirm this information from the survey in the medical record is a unique procedure. So that the prevalence could be used with the relative risk information from the 1960 cohort, we estimated the prevalence in Rochester of those risk factors that were independently significant in the time-dependent covariate analysis, and those prevalence rates are also noted in the table.

Those factors that have a high relative risk and a high prevalence are the ones that have the highest population attributable risk of stroke. Influencing these risks has the greatest possibility for stroke prevention.

Significant Risk Factors for Stroke in Rochester

Risk Factor	R.R.	Prevalence (%) ≥ 50 yrs.	PAR (%)
Age	1.6/10yrs		
Sex	2 (men)		
Hypertension	4	37.2	53
TIA w/o Stroke	3.9	2.7	7
Hypertension Ht dis (w/o CHD)	2.2	3.9	4
Coronary Ht dis (w/o HH)	2.2	11.6	8.5
Congestive Failure	1.7	2.1	1.4
Diabetes	1.7	8.3	5.5
None of these	52.3		

Challenges in Stroke Prevention Research

Philip A. Wolf, M.D.

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Presented on January 5, 1990

Identification of precursors of stroke is the first step in instituting a program for disease prevention. These precursors include "risk factors"—hypertension, diabetes, cigarette smoking, obesity, and predisposing diseases: coronary heart disease, cardiac failure, left ventricular hypertrophy by ECG, and atrial fibrillation. Echocardiographic abnormalities, increased left ventricular mass, and mitral annulus calcification are also stroke precursors.

Two preventive approaches may be taken. The first is a public health approach in which the entire population is informed of the dangers of certain highly prevalent risk factors for disease, and treatment guidelines are outlined. Cigarette smoking, hypertension awareness, and the current cholesterol education programs are examples of this approach. The other approach to disease prevention is more focused and requires treatment by physicians of persons whose risk profile indicates an increased risk of stroke by virtue of predisposing disease.

For the public health approach to be feasible, the risk factor under attack needs to be prevalent in the population and

potent as a disease promoter. One measure of the expected impact of removal of the risk factor on stroke occurrence is the attributable risk that is a function of the prevalence of the condition and its relative risk. For precursors occurring infrequently in the population but with a high relative risk, treatment of these high-risk individuals is in order. Use of a stroke risk profile can help the treating physician identify the high-risk patient predisposed to stroke. However, the relative impact of a risk factor may not be uniform and may be augmented in the presence of other risk factors. For example, risk of stroke in hypertensives is substantially increased in the presence of other risk factors such as cigarette smoking or heart disease. Furthermore, risk factors may vary in their impact in men and women and at different ages. Use of the stroke risk function enables the treating physician to determine the conditional probability of stroke in the individual patient taking sex, blood pressure, cigarette smoking, diabetes, prior cardiovascular disease, LVH by ECG, or atrial fibrillation into account.

Prevention of Ultraviolet-Induced Skin Damage

David R. Bickers, M.D.

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Presented on April 5, 1990

Sunlight is a ubiquitous physical agent present in the environment over all of the planet, and human skin exposure to this form of energy is clearly associated with a spectrum of malignant and nonmalignant effects, some of which lead to dermatologic disease. Solar radiation reaching the Earth's surface includes the ultraviolet, the visible, and the infrared. The shorter highly energetic portion of the ultraviolet known as the ultraviolet B (UVB) is most efficient in evoking erythema (sunburn) and nonmelanoma skin cancer (basal cell and squamous cell) carcinoma and probably melanoma as well. UVB is capable of generating a variety of DNA photoproducts that are mutagenic, and these may result in oncogene activation that is relevant to cancer induction. Extensive epidemiologic studies have verified that chronic exposure to sunlight is directly linked to the development of malignancy. Perhaps the best data in this regard have come from evaluation of British migrants to Australia in whom increased nonmelanoma skin cancer has occurred presumably because of geographic and climatological differences that result in dramatic increases in cumulative sun exposure. Interestingly, the incidence of solar keratosis, a probable precursor of squamous cell carcinoma, is relatively low among those migrants who arrived in Australia after the age of 20 years whereas the incidence in those migrating before the age of 20 years increases with age and eventually exceeds the incidence among the Australian-born population. These observations support the generally accepted concept that the risk of nonmelanoma skin cancer directly relates to total cumulative lifetime exposure to sunlight.

A major challenge is to diminish the risk of cumulative injury to the skin caused by chronic sun exposure. Strategies to deal with this challenge include the more extensive use of proper clothing made of tightly woven fabrics with long sleeves, long pants, and wide-brimmed hats. The use of photoprotective chemical and physical sunscreens that absorb the ultraviolet can diminish the risk of malignant degeneration. Sufficient protection is afforded by sunscreen preparations with a sun protection factor (SPF) of at least 15. In addition, repeated applications of these agents during outdoor activities must be emphasized. Efforts to limit sun exposure, particularly in children, are essential and have not been adequately stressed. Children are estimated to receive 3 to 4 times more UVB on average than do adults and more than 50 percent of lifetime exposure to sunlight occurs before age 18 years. These facts emphasize the need to educate parents and schools about strategies to reduce sun exposure in childhood and adolescence such as moving recreational times to early morning and late afternoon hours, constructing shaded play areas to diminish direct sun exposure, and making sunscreens available to the largest number of people. Thus, addressing behavioral issues should be a major component of public policy aimed at diminishing the risk of sunlight-induced injury. In addition, the effects of these interventions will require adequate management and monitoring using sound epidemiological information systems to assess their impact. With this multifaceted approach to prevention it should be possible to achieve substantial progress in diminishing the risk of the most common form of human malignancy.

Oral Health Effects of Tobacco Use in U.S. Teenagers, 1986-87

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Presented on April 10, 1990

In the 1986-87 school year, the NIDR conducted the second of a series of national surveys of the oral health of U.S. schoolchildren. The survey entailed a national multistage probability sample weighted to represent U.S. schoolchildren in grades K-12. In addition to examinations for dental caries and periodontal health, children received an assessment of the oral mucosa to determine the prevalence of soft tissue pathology. Children in grades 6-12 were also interviewed to determine their past and present use of tobacco in all forms. Examination and interview data from about 20,000 children in grades 6-12 were analyzed to examine the relation between tobacco use and the occurrence of mucosal pathology in adolescents and teenagers.

Overall, about 16 percent of the children reported the past or present use of tobacco, including smoking and smokeless tobacco products. Use was reported by 22 percent of males and 10 percent of females. Whites were almost four times as likely to be users than nonwhites. Prevalence of history of use was about 10 percent for cigarettes, 5 percent for snuff, and 5 percent for chewing tobacco. Use of cigarettes showed no difference by gender, whereas for smokeless tobacco,

males reported use almost 20 times more frequently than females.

Current tobacco use increased from less than 1 percent in sixth graders to almost 17 percent in high school seniors. About 12 percent of seniors reported current use of cigarettes and 6 percent reported smokeless tobacco use. Smokeless tobacco use varied by geographic region, with the New England region having the lowest use and the Southwest having the highest.

Oral examination findings showed that smokeless tobacco-associated mucosal lesions were the third most frequently reported oral pathology, after aphthous ulcers and herpes labialis. These lesions were more prevalent in white males than in other population groups, corresponding to the reported use patterns for smokeless tobacco. Preliminary analysis showed that about 29 percent of smokeless tobacco users had a clinically visible lesion at the time of examination. Lesions were present in about 38 percent of those who used only snuff and in 16 percent of those using only chewing tobacco. A summary of daily use patterns by product type showed that snuff users were more likely to be daily users than tobacco chewers.

Menopausal Symptomatology and Symptom Relief

Nancy E. Avis, Ph.D., M.S.Hyg.

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Presented on May 15, 1990

This presentation addresses the use of estrogen replacement therapy (ERT) for the treatment of menopausal symptoms. To place the use of ERT into proper context and to evaluate the clinical trials designed to determine its effectiveness, it is necessary to examine the symptoms associated with menopause, their prevalence in general populations, and percentages of women who seek treatment because of them,

as well as the prevalence of ERT use and characteristics of women placed on ERT. Research consistently shows that the majority of women experience vasomotor symptoms as they go through menopause. For most women, however, these symptoms are not particularly bothersome and are transitory. Only about 20 percent of women reporting symptoms (excluding those with surgical menopause) seek treatment for

these symptoms. The prevalence of ERT use in general populations averages between 5 percent and 8 percent for naturally postmenopausal women. Although clinical trials have shown that unopposed estrogens, as well as estrogen combined with progesterone, can effectively relieve vasomotor symptoms, all hormone therapies have some negative side effects and/or risks that must be weighed against the symptom relief. Furthermore, the degrees of effectiveness for the general population are probably exaggerated. Because women participating in most trials report severe vasomotor disturbances and are seeking treatment because of them, they are not representative of the general

population of women. Furthermore, most trials include both surgically and naturally postmenopausal women without considering type of menopause in analysis. Finally, studies that have included a placebo control have often found a significant placebo effect and have not considered the net benefit of ERT over and above that of a placebo. Thus, these clinical trials are conducted on an atypical subgroup of menopausal women, and it is not known how generalizable results are to other women. These epidemiological data are important considerations in any evaluation of risks and benefits of ERT.

Estrogen Replacement Therapy: Risks and Benefits

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Johns Hopkins University

Presented on May 15, 1990

This presentation reviews the currently published evidence regarding the association between noncontraceptive estrogen use and risk of cardiovascular disease (CVD) in women and assesses whether the evidence available meets epidemiologic criteria for causality. Nearly all of the studies of noncontraception estrogen use and CVD examined in this report demonstrate a protective effect of estrogen use in women. Qualitative evaluation of the published reports suggests a 40 percent to 50 percent reduction in CVD risk among estrogen users. When the studies are evaluated in light of causal criteria, nearly all of the criteria are met.

However, two unanswered questions need to be addressed. First, it is unknown whether the addition of a progestin to an

estrogen regimen alters the protective effect of estrogen on CVD risk. Because progestins are frequently prescribed to women taking estrogen therapy, and because progestins adversely influence lipoprotein levels, the protective effect of unopposed estrogen use may be blunted by the addition of these hormones. Second, estrogen given transdermally, or by other nonoral routes, may not have the same beneficial effect on CVD risk as oral agents.

Because cardiovascular disease is the number one cause of death in postmenopausal women, and because estrogen use probably reduces the risk of CVD by 40 to 50 percent, estrogen therapy ought to be considered as a preventive therapy for CVD in postmenopausal women.

Effect of Estrogens and Progestins on Risk of Endometrial and Breast Cancer

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Endometrial Cancer

Several lines of evidence indicate that estrogen replacement therapy (ERT) causes endometrial cancer: (1) estrogen stimulates division of endometrial cells, particularly in the follicular phase of the menstrual cycle; (2) estrogen is associated with adenomatous endometrial hyperplasia, a precancerous lesion; (3) an increase in estrogen prescriptions in the 1970's paralleled an increased incidence of endometrial cancer; and (4) findings from case-control and cohort studies consistently show increased risk for endometrial cancer in postmenopausal women treated with estrogen. Risk of endometrial cancer is approximately twofold to fourfold higher in ERT users and increases with increasing dose and duration of use. An increase in mortality from ERT has not been shown. The increased incidence of endometrial cancer is the major confirmed adverse effect of unopposed ERT. Endometrial hyperplasia and cancer can be treated with progestins, and risk for endometrial cancer is reduced in combination with oral contraceptive users, suggesting that a progestin added to estrogen replacement therapy (PERT) may protect against endometrial cancer. Several cohort studies and one small controlled trial (all with methodologic shortcomings) suggest that risk of endometrial cancer is not increased in postmenopausal women treated with PERT. Based on studies of endometrial hyperplasia, 10 to 12 days of progestin treatment per month appear to be maximally protective.

Breast Cancer

Because the breast, like the uterus, is an estrogen responsive organ, the finding that ERT causes endometrial cancer

suggests that it might also cause breast cancer. Other evidence includes the fact that many of the established risk factors for breast cancer are related to estrogen exposure, that estrogen acts as a breast cancer promoter in rats treated with carcinogens, and that breast cancer can be treated with antiestrogens such as tamoxifen. Multiple case-control and cohort studies of the risk of breast cancer in women treated with ERT have provided conflicting and inconclusive results. The overwhelming majority show no increased risk for breast cancer among ever users of ERT, but several indicate that risk might increase modestly after 15 to 20 years of use, with high-dose use, or in certain subgroups of women. Progesterone is often added to the estrogen regimen in women who have had a hysterectomy (and are thus not at risk for endometrial cancer) in the hope that PERT might be protective for breast cancer as well as endometrial cancer. There is some reason to believe that progestins might increase the risk of breast cancer, however, because the highest rate of division of breast epithelial cells occurs in the luteal phase, when levels of both estrogen and progesterone are relatively high. The few epidemiologic studies addressing the effect of PERT on breast cancer risk have been conflicting and suffer from methodologic problems. There is no evidence to support adding a progestin to ERT in women without a uterus.

Although effective in eliminating the increased risk of endometrial hyperplasia and cancer due to estrogen therapy, the net effect of treatment with added progestins may not be beneficial, even in women with a uterus. Knowledge of the long-term impact of progestins on breast cancer is critical to this risk-benefit assessment.

Estrogen Efficacy and Side Effects in Prevention and Treatment of Osteoporosis

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Abundant evidence from several well-controlled studies confirms that estrogen therapy prevents the bone loss that occurs in estrogen-deficient women. Our data demonstrate that estrogen treatment of postmenopausal women prevents peripheral cortical bone loss for as long as estrogens are given (at least 10 to 12 years) and that bone loss begins again when therapy is withdrawn. For women on a usual dietary calcium intake, the minimum effective dose is 0.625 Premarin per day. The addition of a progestogen does not appear to reduce the effectiveness of estrogens and indeed certain progestogens may also reduce bone loss in postmenopausal

women. Recently, we showed that after 10 years of therapy, bone mineral density of the lumbar spine by DPA is 29 percent greater in the estrogen-treated group than in placebo-treated women, and hip density is 12 percent greater. It is not clear if this difference between sites is caused by more rapid loss of bone in the spine than in the hip, or whether estrogen prevention is less effective in the hip. Postmenopausal estrogen exposure reduces hip fracture, in several epidemiological studies, suggesting that the former explanation is the correct one. However, prospective data clearly are needed.

Prevention of Genital Herpes

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Presented on June 8, 1990

Genital herpes is an acute and recurring infection caused by herpes simplex virus type 2 (HSV-2) and occasionally by HSV-1. An estimated 20 to 40 million Americans are infected, only one-third to one-half of whom ever experience recognizable symptoms or signs of the disease. Symptomatic primary and recurrent infections are effectively treated with acyclovir. Frequently recurring genital outbreaks are well managed with chronic suppressive acyclovir therapy, an approach that has proven remarkably well tolerated for years.

Genital herpes is emotionally and socially distressing but is not physically debilitating, except during severe primary episodes and in immunocompromised people such as AIDS patients, in whom it may be severely painful, chronic, and even resistant to acyclovir treatment.

A devastating but rare complication of genital herpes follows transmission of virus during delivery. The infected baby has a high likelihood of a severely impairing or even fatal encephalitis. Current recommendations are to carefully examine during labor any women with a history of genital herpes and to perform cesarean section if signs or symptoms of herpes are present. Otherwise, vaginal delivery is appropriate.

Unfortunately, herpes is often transmitted in the absence of symptoms. So, efforts to prevent transmission by avoiding contact while symptomatic are incompletely successful. There are several alternative strategies for herpes prevention that are worth considering and testing. One entails the use of antiviral drugs like acyclovir as a true prophylactic agent. Studies in mice showed it possible to completely prevent disease and the establishment of virus latency if acyclovir

were given at, or very shortly after, the time of virus inoculation. This approach can be tested in humans but even if effective is subject to abuse and arouses concerns about fostering more drug resistance.

Vaccines for HSV-1 and 2 have long been sought, but no candidates have yet emerged as useful in controlled trials. New vaccine strategies are more promising. The major lines of current investigation involve live recombinants of HSV-1 or vaccinia that have been engineered to contain HSV-2

glycoprotein genes, while other candidate vaccines consist of purified recombinant HSV-2 glycoproteins themselves. Human trials with some of these new vaccines are under way.

Genital herpes remains a common and distressing public health problem that is now amenable to control through diagnosis, education, and treatment. Rational means of prevention continue to evolve.

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